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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C12N 15/51, C12Q 1/68 C12N 15/40, C12Q 1/70 A61K 39/29, C07K 13/00 G01N 33/576	A2	(11) International Publication Number: WO 92/19743 (43) International Publication Date: 12 November 1992 (12.11.92)
(21) International Application Number: PCT/US92/04036 (22) International Filing Date: 8 May 1992 (08.05.92) (30) Priority data: 697,326 8 May 1991 (08.05.91) US (71) Applicant: CHIRON CORPORATION [US/US]; 4560 Horton Street, Emeryville, CA 94608 (US). (72) Inventors: CHA, Tai-An ; 964 Springview Circle, San Ramon, CA 94583 (US). BEALL, Eileen ; 1150 Lincoln Avenue, # 5, Walnut Creek, CA 94596 (US). IRVINE, Bruce ; 3401 El Monte Drive, Concord, CA 94519 (US). KOLBERG, Janice ; 131 Scots Valley, Hercules, CA 94547 (US). URDEA, Michael, S. ; 100 Bunce Meadow Road, Alamo, CA 94501 (US).		(74) Agent: JANIUK, Anthony, J.; Wolf, Greenfield & Sacks, 600 Atlantic Avenue, Boston, MA 02210 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent). Published <i>Without international search report and to be republished upon receipt of that report.</i>

(54) Title: HCV GENOMIC SEQUENCES FOR DIAGNOSTICS AND THERAPEUTICS**(57) Abstract**

The present application features nucleic acid, peptide and antibody compositions relating to genotypes of hepatitis C virus and methods of using such compositions for diagnostic and therapeutic purposes.

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HCV GENOMIC SEQUENCES FOR
DIAGNOSTICS AND THERAPEUTICS

This application is a continuation-in-part of U.S.
5 Serial No. 07/697,326 entitled "Polynucleotide Probes
Useful for Screening for Hepatitis C Virus, filed May
8, 1991.

Technical Field

10 The invention relates to compositions and methods
for the detection and treatment of hepatitis C virus,
(HCV) infection, formerly referred to as blood-borne
non-A, non-B hepatitis virus (NANBV) infection. More
specifically, embodiments of the present invention
15 feature compositions and methods for the detection of
HCV, and for the development of vaccines for the
prophylactic treatment of infections of HCV, and
development of antibody products for conveying passive
immunity to HCV.

20

Background of the Invention

The prototype isolate of HCV was characterized in
U.S. Patent Application Serial No. 122,714 (See also
EPO Publication No. 318,216). As used herein, the term
25 "HCV" includes new isolates of the same viral species.
The term "HCV-1" referred to in U.S. Patent Application
Serial No. 122,714.

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HCV is a transmissible disease distinguishable from other forms of viral-associated liver diseases, including that caused by the known hepatitis viruses, i.e., hepatitis A virus (HAV), hepatitis B virus (HBV), and delta hepatitis virus (HDV), as well as the hepatitis induced by cytomegalovirus (CMV) or Epstein-Barr virus (EBV). HCV was first identified in individuals who had received blood transfusions.

The demand for sensitive, specific methods for screening and identifying carriers of HCV and HCV contaminated blood or blood products is significant. Post-transfusion hepatitis (PTH) occurs in approximately 10% of transfused patients, and HCV accounts for up to 90% of these cases. The disease frequently progresses to chronic liver damage (25-55%).

Patient care as well as the prevention of transmission of HCV by blood and blood products or by close personal contact require reliable screening, diagnostic and prognostic tools to detect nucleic acids, antigens and antibodies related to HCV.

Information in this application suggests the HCV has several genotypes. That is, the genetic information of the HCV virus may not be totally identical for all HCV, but encompasses groups with differing genetic information.

Genetic information is stored in thread-like molecules of DNA and RNA. DNA consists of covalently

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linked chains of deoxyribonucleotides and RNA consists of covalently linked chains of ribonucleotides. Each nucleotide is characterized by one of four bases: adenine (A), guanine (G), thymine (T), and cytosine (C). The bases are complementary in the sense that, due to the orientation of functional groups, certain base pairs attract and bond to each other through hydrogen bonding and π -stacking interactions. Adenine in one strand of DNA pairs with thymine in an opposing complementary strand. Guanine in one strand of DNA pairs with cytosine in an opposing complementary strand. In RNA, the thymine base is replaced by uracil (U) which pairs with adenine in an opposing complementary strand. The genetic code of living organism is carried in the sequence of base pairs. Living cells interpret, transcribe and translate the information of nucleic acid to make proteins and peptides.

The HCV genome is comprised of a single positive strand of RNA. The HCV genome possesses a continuous, translational open reading frame (ORF) that encodes a polyprotein of about 3,000 amino acids. In the ORF, the structural protein(s) appear to be encoded in approximately the first quarter of the N-terminus region, with the majority of the polyprotein responsible for non-structural proteins.

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The HCV polyprotein comprises, from the amino terminus to the carboxy terminus, the nucleocapsid protein (C), the envelope protein (E), and the non-structural proteins (NS) 1, 2 (b), 3, 4 (b), and 5.

5 HCV of differing genotypes may encode for proteins which present an altered response to host immune systems. HCV of differing genotypes may be difficult to detect by immuno diagnostic techniques and nucleic acid probe techniques which are not specifically
10 directed to such genotype.

Definitions for selected terms used in the application are set forth below to facilitate an understanding of the invention. The term "corresponding" means homologous to or complementary to
15 a particular sequence of nucleic acid. As between nucleic acids and peptides, corresponding refers to amino acids of a peptide in an order derived from the sequence of a nucleic acid or its complement.

The term "non-naturally occurring nucleic acid"
20 refers to a portion of genomic nucleic acid, cDNA, semisynthetic nucleic acid, or synthetic origin nucleic acid which, by virtue of its origin or manipulation: (1) is not associated with all of a nucleic acid with which it is associated in nature, (2) is linked to a
25 nucleic acid or other chemical agent other than that to

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which it is linked in nature, or (3) does not occur in nature.

Similarly the term, "a non-naturally occurring peptide" refers to a portion of a large naturally occurring peptide or protein, or semi-synthetic or synthetic peptide, which by virtue of its origin or manipulation (1) is not associated with all of a peptide with which it is associated in nature, (2) is linked to peptides, functional groups or chemical agents other than that to which it is linked in nature, or (3) does not occur in nature.

The term "primer" refers to a nucleic acid which is capable of initiating the synthesis of a larger nucleic acid when placed under appropriate conditions. The primer will be completely or substantially complementary to a region of the nucleic acid to be copied. Thus, under conditions conducive to hybridization, the primer will anneal to a complementary region of a larger nucleic acid. Upon addition of suitable reactants, the primer is extended by the polymerizing agent to form a copy of the larger nucleic acid.

The term "binding pair" refers to any pair of molecules which exhibit mutual affinity or binding capacity. For the purposes of the present application, the term "ligand" will refer to one molecule of the binding pair, and the term "antiligand" or "receptor"

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or "target" will refer to the opposite molecule of the binding pair. For example, with respect to nucleic acids, a binding pair may comprise two complementary nucleic acids. One of the nucleic acids may be
5 designated the ligand and the other strand is designated the antiligand receptor or target. The designation of ligand or antiligand is a matter of arbitrary convenience. Other binding pairs comprise, by way of example, antigens and antibodies, drugs and
10 drug receptor sites and enzymes and enzyme substrates, to name a few.

The term "label" refers to a molecular moiety capable of detection including, by way of example, without limitation, radioactive isotopes, enzymes,
15 luminescent agents, precipitating agents, and dyes.

The term "support" includes conventional supports such as filters and membranes as well as retrievable supports which can be substantially dispersed within a medium and removed or separated from the medium by
20 immobilization, filtering, partitioning, or the like. The term "support means" refers to supports capable of being associated to nucleic acids, peptides or antibodies by binding partners, or covalent or noncovalent linkages.

25 A number of HCV strains and isolates have been identified. When compared with the sequence of the original isolate derived from the USA ("HCV-1"; see

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Q.-L. Choo et al. (1989) Science 244:359-362, Q.-L. Choo et al. (1990) Brit. Med. Bull. 46:423-441, Q.-L. Choo et al., Proc. Natl. Acad. Sci. 88:2451-2455 (1991), and E.P.O. Patent Publication No. 318,216, cited supra), it was found that a Japanese isolate ("HCV J1") differed significantly in both nucleotide and polypeptide sequence within the NS3 and NS4 regions. This conclusion was later extended to the NS5 and envelope (E1/S and E2/NS1) regions (see K. Takeuchi et al., J. Gen. Virol. (1990) 71:3027-3033, Y. Kubo, Nucl. Acids. Res. (1989) 17:10367-10372, and K. Takeuchi et al., Gene (1990) 91:287-291). The former group of isolates, originally identified in the United States, is termed "Genotype I" throughout the present disclosure, while the latter group of isolates, initially identified in Japan, is termed "Genotype II" herein.

Brief Description of the Invention

The present invention features compositions of matter comprising nucleic acids and peptides corresponding to the HCV viral genome which define different genotypes. The present invention also features methods of using the compositions corresponding to sequences of the HCV viral genome which define different genotypes described herein.

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A. Nucleic acid compositions

The nucleic acid of the present invention, corresponding to the HCV viral genome which define different genotypes, have utility as probes in nucleic acid hybridization assays, as primers for reactions involving the synthesis of nucleic acid, as binding partners for separating HCV viral nucleic acid from other constituents which may be present, and as anti-sense nucleic acid for preventing the transcription or translation of viral nucleic acid.

One embodiment of the present invention features a composition comprising a non-naturally occurring nucleic acid having a nucleic acid sequence of at least eight nucleotides corresponding to a non-HCV-1 nucleotide sequence of the hepatitis C viral genome. Preferably, the nucleotide sequence is selected from a sequence present in at least one region consisting of the NS5 region, envelope 1 region, 5'UT region, and the core region.

Preferably, with respect to sequences which correspond to the NS5 region, the sequence is selected from a sequence within a sequence numbered 2-22. The sequence numbered 1 corresponds to HCV-1. Sequences numbered 1-22 are defined in the Sequence Listing of the application.

Preferably, with respect to sequences corresponding to the envelope 1 region, the sequence is

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selected from a sequence within sequences numbered 24-32. Sequence No. 23 corresponds to HCV-1. Sequences numbered 23-32 are set forth in the Sequence Listing of the application.

5 Preferably, with respect to the sequences which correspond to the 5'UT regions, the sequence is selected from a sequence within sequences numbered 34-51. Sequence No. 33 corresponds to HCV-1. Sequence No. 33-51 are set forth in the Sequence Listing of this
10 application.

 Preferably, with respect to the sequences which correspond to the core region, the sequence is selected from a sequence within the sequences numbered 53-66. Sequence No. 52 corresponds to HCV-1. Sequences 52-66
15 are set forth in the Sequence Listing of this application.

 The compositions of the present invention form hybridization products with nucleic acid corresponding to different genotypes of HCV.

20 HCV has at least five genotypes, which will be referred to in this application by the designations GI-GV. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The second genotype, GII, is exemplified by the sequences
25 numbered 7-12, 26-28, 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV,

is exemplified by sequences numbered 20-22, and 29-31 and 48-49. The fifth genotype, GV, is exemplified by sequences numbered 18, 19, 50 and 51.

One embodiment of the present invention features
5 compositions comprising a nucleic acid having a sequence corresponding to one or more sequences which exemplify a genotype of HCV.

B. Method of forming a Hybridization Product

10 Embodiments of the present invention also feature a method of forming a hybridization product with nucleic acid having a sequence corresponding to HCV nucleic acid. One method comprises the steps of placing a non-naturally occurring nucleic acid having a
15 non-HCV-1 sequence corresponding to HCV nucleic acid under conditions in which hybridization may occur. The non-naturally occurring nucleic acid is capable of forming a hybridization product with HCV nucleic acid, under hybridization conditions. The method further
20 comprises the step of imposing hybridization conditions to form a hybridization product in the presence of nucleic acid corresponding to a region of the HCV genome.

The formation of a hybridization product has
25 utility for detecting the presence of one or more genotypes of HCV. Preferably, the non-naturally occurring nucleic acid forms a hybridization product

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with nucleic acid of HCV in one or more regions comprising the NS5 region, envelope 1 region, 5'UT region and the core region. To detect the hybridization product, it is useful to associate the non-naturally occurring nucleic acid with a label. The formation of the hybridization product is detected by separating the hybridization product from labeled non-naturally occurring nucleic acid, which has not formed a hybridization product.

The formation of a hybridization product has utility as a means of separating one or more genotypes of HCV nucleic acid from other constituents potentially present. For such applications, it is useful to associate the non-naturally occurring nucleic acid with a support for separating the resultant hybridization product from the the other constituents.

Nucleic acid "sandwich assays" employ one nucleic acid associated with a label and a second nucleic acid associated with a support. An embodiment of the present invention features a sandwich assay comprising two nucleic acids, both have sequences which correspond to HCV nucleic acids; however, at least one non-naturally occurring nucleic acid has a sequence corresponding to non-HCV-1 HCV nucleic acid. At least one nucleic acid is capable of associating with a label, and the other is capable of associating with a support. The support associated non-naturally

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occurring nucleic acid is used to separate the hybridization products which include an HCV nucleic acid and the non-naturally occurring nucleic acid having a non-HCV-1 sequence.

5 One embodiment of the present invention features a method of detecting one or more genotypes of HCV. The method comprises the steps of placing a non-naturally occurring nucleic acid under conditions which hybridization may occur. The non-naturally occurring
10 nucleic acid is capable of forming a hybridization product with nucleic acid from one or more genotypes of HCV. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The second genotype, GII, is exemplified by the sequences
15 numbered 7-12, 26-28, 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV, is exemplified sequences numbered 20-22 and 29-31. The fifth genotype, GV, is exemplified by sequences
20 numbered 18, 19, 50 and 51.

 The hybridization product of HCV nucleic acid with a non-naturally occurring nucleic acid having non-HCV-1 sequence corresponding to sequences within the HCV genome has utility for priming a reaction for the
25 synthesis of nucleic acid.

 The hybridization product of HCV nucleic acid with a non-naturally occurring nucleic acid having a

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sequence corresponding to a particular genotype of HCV has utility for priming a reaction for the synthesis of nucleic acid of such genotype. In one embodiment, the synthesized nucleic acid is indicative of the presence
5 of one or more genotypes of HCV.

The synthesis of nucleic acid may also facilitate cloning of the nucleic acid into expression vectors which synthesize viral proteins.

Embodiments of the present methods have utility as
10 anti-sense agents for preventing the transcription or translation of viral nucleic acid. The formation of a hybridization product of a non-naturally occurring nucleic acid having sequences which correspond to a particular genotype of HCV genomic sequencing with HCV
15 nucleic acid may block translation or transcription of such genotype. Therapeutic agents can be engineered to include all five genotypes for inclusivity.

C. Peptide and antibody composition

A further embodiment of the present invention
20 features a composition of matter comprising a non-naturally occurring peptide of three or more amino acids corresponding to a nucleic acid having a non-HCV-1 sequence. Preferably, the non-HCV-1 sequence corresponds with a sequence within one or more regions
25 consisting of the NS5 region, the envelope 1 region, the 5'UT region, and the core region.

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Preferably, with respect to peptides corresponding to a nucleic acid having a non-HCV-1 sequence of the NS5 region, the sequence is within sequences numbered 2-22. The sequence numbered 1 corresponds to HCV-1.
5 Sequences numbered 1-22 are set forth in the Sequence Listing.

Preferably, with respect to peptides corresponding to a nucleic acid having a non-HCV-1 sequence of the envelope 1 region, the sequence is within sequences
10 numbered 24-32. The sequence numbered 23 corresponds to HCV-1. Sequences numbered 23-32 are set forth in the Sequence Listing.

Preferably, with respect to peptides corresponding to a nucleic acid having a non-HCV-1 sequence directed
15 to the core region, the sequence is within sequences numbered 53-66. Sequence numbered 52 corresponds to HCV-1. Sequences numbered 52-66 are set forth in the Sequence Listing.

The further embodiment of the present invention
20 features peptide compositions corresponding to nucleic acid sequences of a genotype of HCV. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The second genotype, GII, is exemplified by the sequences numbered 7-12, 26-28,
25 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV, is exemplified

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sequences numbered 20-22, 29-31, 48 and 49. The fifth genotype, GV, is exemplified by sequences numbered 18, 19, 50 and 51.

5 The non-naturally occurring peptides of the present invention are useful as a component of a vaccine. The sequence information of the present invention permits the design of vaccines which are inclusive for all or some of the different genotypes of HCV. Directing a vaccine to a particular genotype
10 allows prophylactic treatment to be tailored to maximize the protection to those agents likely to be encountered. Directing a vaccine to more than one genotype allows the vaccine to be more inclusive.

15 The peptide compositions are also useful for the development of specific antibodies to the HCV proteins. One embodiment of the present invention features as a composition of matter, an antibody to peptides corresponding to a non-HCV-1 sequence of the HCV genome. Preferably, the non-HCV-1 sequence is
20 selected from the sequence within a region consisting of the NS5 region, the envelope 1 region, and the core region. There are no peptides associated with the untranslated 5'UT region.

25 Preferably, with respect to antibodies directed to peptides of the NS5 region, the peptide corresponds to a sequence within sequences numbered 2-22. Preferably, with respect to antibodies directed to a peptide

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corresponding to the envelope 1 region, the peptide corresponds to a sequence within sequences numbered 24-32. Preferably, with respect to the antibodies directed to peptides corresponding to the core region, the peptide corresponds to a sequence within sequences numbered 53-66.

Antibodies directed to peptides which reflect a particular genotype have utility for the detection of such genotypes of HCV and therapeutic agents.

One embodiment of the present invention features an antibody directed to a peptide corresponding to nucleic acid having sequences of a particular genotype. The first genotype, GI, is exemplified by sequences numbered 1-6, 23-25, 33-38 and 52-57. The second genotype, GII, is exemplified by the sequences numbered 7-12, 26-28, 39-45 and 58-64. The third genotype, GIII, is exemplified by sequences numbered 13-17, 32, 46-47 and 65-66. The fourth genotype, GIV, is exemplified sequences numbered 20-22, 29-31, 48 and 49. The fifth genotype, GV, is exemplified by sequences numbered 18, 19, 50 and 51.

Individuals skilled in the art will readily recognize that the compositions of the present invention can be packaged with instructions for use in the form of a kit for performing nucleic acid hybridizations or immunochemical reactions.

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The present invention is further described in the following figures which illustrate sequences demonstrating genotypes of HCV. The sequences are designated by numerals 1-145, which numerals and sequences are consistent with the numerals and sequences set forth in the Sequence Listing. Sequences 146 and 147 facilitate the discussion of an assay which numerals and sequences are consistent with the numerals and sequences set forth in the Sequence Listing.

10

Brief Description of the Figures and Sequence Listing

Figure 1 depicts schematically the genetic organization of HCV;

Figure 2 sets forth nucleic acid sequences numbered 1-22 which sequences are derived from the NS5 region of the HCV viral genome;

Figure 3 sets forth nucleic acid sequences numbered 23-32 which sequences are derived from the envelope 1 region of the HCV viral genome;

Figure 4 sets forth nucleic acid sequences numbered 33-51 which sequences are derived from the 5'UT region of the HCV viral genome; and,

Figure 5 sets forth nucleic acid sequences numbered 52-66 which sequences are derived from the core region of the HCV viral genome.

The Sequence Listing sets forth the sequences of sequences numbered 1-147.

Detailed Description of the Invention

The present invention will be described in detail as as nucleic acid having sequences corresponding to the HCV genome and related peptides and binding
5 partners, for diagnostic and therapeutic applications.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, and immunology, which are within the skill of the
10 art. Such techniques are explained fully in the literature. See e.g., Maniatis, Fitsch & Sambrook, Molecular Cloning; A Laboratory Manual (1982); DNA Cloning, Volumes I and II (D.N Glover ed. 1985);
Oligonucleotide Synthesis (M.J. Gait ed, 1984); Nucleic
15 Acid Hybridization (B.D. Hames & S.J. Higgins eds. 1984); the series, Methods in Enzymology (Academic Press, Inc.), particularly Vol. 154 and Vol. 155 (Wu and Grossman, eds.).

The cDNA libraries are derived from nucleic acid
20 sequences present in the plasma of an HCV-infected chimpanzee. The construction of one of these libraries, the "c" library (ATCC No. 40394), is described in PCT Pub. No. WO90/14436. The sequences of the library relevant to the present invention are set
25 forth herein as sequence numbers 1, 23, 33 and 52.

Nucleic acids isolated or synthesized in accordance with features of the present invention are

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useful, by way of example without limitation as probes, primers, anti-sense genes and for developing expression systems for the synthesis of peptides corresponding to such sequences.

5 The nucleic acid sequences described define genotypes of HCV with respect to four regions of the viral genome. Figure 1 depicts schematically the organization of HCV. The four regions of particular interest are the NS5 region, the envelope 1 region, the
10 5'UT region and the core region.

 The sequences set forth in the present application as sequences numbered 1-22 suggest at least five genotypes in the NS5 region. Sequences numbered 1-22 are depicted in Figure 2 as well as the Sequence
15 Listing. Each sequence numbered 1-22 is derived from nucleic acid having 340 nucleotides from the NS5 region.

 The five genotypes are defined by groupings of the sequences defined by sequence numbered 1-22. For convenience, in the present application, the different
20 genotypes will be assigned roman numerals and the letter "G".

 The first genotype (GI) is exemplified by sequences within sequences numbered 1-6. A second genotype (GII) is exemplified by sequences within
25 sequences numbered 7-12. A third genotype (GIII) is exemplified by the sequences within sequences numbered 13-17. A fourth genotype (GIV) is exemplified by

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sequences within sequences numbered 20-22. A fifth genotype (GV) is exemplified by sequences within sequences numbered 18 and 19.

5 The sequences set forth in the present application as sequences numbered 23-32 suggest at least four genotypes in the envelope 1 region of HCV. Sequences numbered 23-32 are depicted in Figure 3 as well as in the Sequence Listing. Each sequence numbered 23-32 is derived from nucleic acid having 100 nucleotides from
10 the envelope 1 region.

A first envelope 1 genotype group (GI) is exemplified by the sequences within the sequences numbered 23-25. A second envelope 1 genotype (GII) region is exemplified by sequences within sequences
15 numbered 26-28. A third envelope 1 genotype (GIII) is exemplified by the sequences within sequences numbered 32. A fourth envelope 1 genotype (GIV) is exemplified by the sequences within sequence numbered 29-31.

The sequences set forth in the present application
20 as sequences numbered 33-51 suggest at least three genotypes in the 5'UT region of HCV. Sequences numbered 33-51 are depicted in Figure 4 as well as in the Sequence Listing. Each sequence numbered 33-51 is derived from the nucleic acid having 252 nucleotides
25 from the 5'UT region, although sequences 50 and 51 are somewhat shorter at approximately 180 nucleotides.

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The first 5'UT genotype (GI) is exemplified by the sequences within sequences numbered 33-38. A second 5'UT genotype (GII) is exemplified by the sequences within sequences numbered 39-45. A third 5'UT genotype (GIII) is exemplified by the sequences within sequences numbered 46-47. A fourth 5'UT genotype (GIV) is exemplified by sequences within sequences numbered 48 and 49. A fifth 5'UT genotype (GV) is exemplified by sequences within sequences numbered 50 and 51.

10 The sequences numbered 48-62 suggest at least three genotypes in the core region of HCV. The sequences numbered 52-66 are depicted in Figure 5 as well as in the Sequence Listing.

15 The first core region genotype (GI) is exemplified by the sequences within sequences numbered 52-57. The second core region genotype (GII) is exemplified by sequences within sequences numbered 58-64. The third core region genotype (GIII) is exemplified by sequences within sequences numbered 65 and 66. Sequences
20 numbered 52-65 are comprised of 549 nucleotides. Sequence numbered 66 is comprised of 510 nucleotides.

The various genotypes described with respect to each region are consistent. That is, HCV having features of the first genotype with respect to the NS5
25 region will substantially conform to features of the first genotype of the envelope 1 region, the 5'UT region and the core region.

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Nucleic acid isolated or synthesized in accordance with the sequences set forth in sequence numbers 1-66 are useful as probes, primers, capture ligands and anti-sense agents. As probes, primers, capture ligands and anti-sense agents, the nucleic acid will normally comprise approximately eight or more nucleotides for specificity as well as the ability to form stable hybridization products.

10 Probes

A nucleic acid isolated or synthesized in accordance with a sequence defining a particular genotype of a region of the HCV genome can be used as a probe to detect such genotype or used in combination with other nucleic acid probes to detect substantially all genotypes of HCV.

With the sequence information set forth in the present application, sequences of eight or more nucleotides are identified which provide the desired inclusivity and exclusivity with respect to various genotypes within HCV, and extraneous nucleic acid sequences likely to be encountered during hybridization conditions.

Individuals skilled in the art will readily recognize that the nucleic acid sequences, for use as probes, can be provided with a label to facilitate detection of a hybridization product.

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Capture Ligand

For use as a capture ligand, the nucleic acid selected in the manner described above with respect to probes, can be readily associated with supports. The manner in which nucleic acid is associated with supports is well known. Nucleic acid having sequences corresponding to a sequence within sequences numbered 1-66 have utility to separate viral nucleic acid of one genotype from the nucleic acid of HCV of a different genotype. Nucleic acid isolated or synthesized in accordance with sequences within sequences numbered 1-66, used in combinations, have utility to capture substantially all nucleic acid of all HCV genotypes.

15 Primers

Nucleic acid isolated or synthesized in accordance with the sequences described herein have utility as primers for the amplification of HCV sequences. With respect to polymerase chain reaction (PCR) techniques, nucleic acid sequences of eight or more nucleotides corresponding to one or more sequences of sequences numbered 1-66 have utility in conjunction with suitable enzymes and reagents to create copies of the viral nucleic acid. A plurality of primers having different sequences corresponding to more than one genotype can be used to create copies of viral nucleic acid for such genotypes.

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The copies can be used in diagnostic assays to detect HCV virus. The copies can also be incorporated into cloning and expression vectors to generate polypeptides corresponding to the nucleic acid synthesized by PCR, as will be described in greater detail below.

Anti-sense

Nucleic acid isolated or synthesized in accordance with the sequences described herein have utility as anti-sense genes to prevent the expression of HCV.

Nucleic acid corresponding to a genotype of HCV is loaded into a suitable carrier such as a liposome for introduction into a cell infected with HCV. A nucleic acid having eight or more nucleotides is capable of binding to viral nucleic acid or viral messenger RNA. Preferably, the anti-sense nucleic acid is comprised of 30 or more nucleotides to provide necessary stability of a hybridization product of viral nucleic acid or viral messenger RNA. Methods for loading anti-sense nucleic acid is known in the art as exemplified by U.S. Patent 4,241,046 issued December 23, 1980 to Papahadjopoulos et al.

Peptide Synthesis

Nucleic acid isolated or synthesized in accordance with the sequences described herein have utility to

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generate peptides. The sequences exemplified by sequences numbered 1-32 and 52-66 can be cloned into suitable vectors or used to isolate nucleic acid. The isolated nucleic acid is combined with suitable DNA linkers and cloned into a suitable vector. The vector can be used to transform a suitable host organism such as E. coli and the peptide encoded by the sequences isolated.

Molecular cloning techniques are described in the text Molecular Cloning: A Laboratory Manual, Maniatis et al., Coldspring Harbor Laboratory (1982).

The isolated peptide has utility as an antigenic substance for the development of vaccines and antibodies directed to the particular genotype of HCV.

Vaccines and Antibodies

The peptide materials of the present invention have utility for the development of antibodies and vaccines.

The availability of cDNA sequences, or nucleotide sequences derived therefrom (including segments and modifications of the sequence), permits the construction of expression vectors encoding antigenically active regions of the peptide encoded in either strand. The antigenically active regions may be derived from the NS5 region, envelope 1 regions, and the core region.

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Fragments encoding the desired peptides are derived from the cDNA clones using conventional restriction digestion or by synthetic methods, and are ligated into vectors which may, for example, contain portions of fusion sequences such as beta galactosidase or superoxide dismutase (SOD), preferably SOD. Methods and vectors which are useful for the production of polypeptides which contain fusion sequences of SOD are described in European Patent Office Publication number 0196056, published October 1, 1986.

Any desired portion of the HCV cDNA containing an open reading frame, in either sense strand, can be obtained as a recombinant peptide, such as a mature or fusion protein; alternatively, a peptide encoded in the cDNA can be provided by chemical synthesis.

The DNA encoding the desired peptide, whether in fused or mature form, and whether or not containing a signal sequence to permit secretion, may be ligated into expression vectors suitable for any convenient host. Both eukaryotic and prokaryotic host systems are presently used in forming recombinant peptides. The peptide is then isolated from lysed cells or from the culture medium and purified to the extent needed for its intended use. Purification may be by techniques known in the art, for example, differential extraction, salt fractionation, chromatography on ion exchange resins, affinity chromatography, centrifugation, and

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the like. See, for example, Methods in Enzymology for a variety of methods for purifying proteins. Such peptides can be used as diagnostics, or those which give rise to neutralizing antibodies may be formulated into vaccines. Antibodies raised against these peptides can also be used as diagnostics, or for passive immunotherapy or for isolating and identifying HCV.

An antigenic region of a peptide is generally relatively small--typically 8 to 10 amino acids or less in length. Fragments of as few as 5 amino acids may characterize an antigenic region. These segments may correspond to NS5 region, envelope 1 region, and the core region of the HCV genome. The 5'UT region is not known to be translated. Accordingly, using the cDNAs of such regions, DNAs encoding short segments of HCV peptides corresponding to such regions can be expressed recombinantly either as fusion proteins, or as isolated peptides. In addition, short amino acid sequences can be conveniently obtained by chemical synthesis. In instances wherein the synthesized peptide is correctly configured so as to provide the correct epitope, but is too small to be immunogenic, the peptide may be linked to a suitable carrier.

A number of techniques for obtaining such linkage are known in the art, including the formation of disulfide linkages using N-succinimidyl-3-(2-

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pyridylthio)propionate (SPDP) and succinimidyl
4-(N-maleimido-methyl)cyclohexane-1-carboxylate (SMCC)
obtained from Pierce Company, Rockford, Illinois, (if
the peptide lacks a sulfhydryl group, this can be
5 provided by addition of a cysteine residue). These
reagents create a disulfide linkage between themselves
and peptide cysteine residues on one protein and an
amide linkage through the epsilon-amino on a lysine, or
other free amino group in the other. A variety of such
10 disulfide/amide-forming agents are known. See, for
example, Immun Rev (1982) 62:185. Other bifunctional
coupling agents form a thioether rather than a
disulfide linkage. Many of these thio-ether-forming
agents are commercially available and include reactive
15 esters of 6-maleimidocaprioc acid, 2-bromoacetic acid,
2-iodoacetic acid, 4-N-maleimido-methyl)cyclohexane-1-
carboxylic acid, and the like. The carboxyl groups can
be activated by combining them with succinimide or
1-hydroxyl-2 nitro-4-sulfonic acid, sodium salt.
20 Additional methods of coupling antigens employs the
rotavirus/"binding peptide" system described in EPO
Pub. No. 259,149, the disclosure of which is
incorporated herein by reference. The foregoing list
is not meant to be exhaustive, and modifications of the
25 named compounds can clearly be used.

Any carrier may be used which does not itself
induce the production of antibodies harmful to the

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host. Suitable carriers are typically large, slowly metabolized macromolecules such as proteins; polysaccharides, such as latex functionalized Sepharose, agarose, cellulose, cellulose beads and the like; polymeric amino acids, such as polyglutamic acid, polylysine, and the like; amino acid copolymers; and inactive virus particles. Especially useful protein substrates are serum albumins, keyhole limpet hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, and other proteins well known to those skilled in the art.

Peptides comprising HCV amino acid sequences encoding at least one viral epitope derived from the NS5, envelope 1, and core region are useful immunological reagents. The 5'UT region is not known to be translated. For example, peptides comprising such truncated sequences can be used as reagents in an immunoassay. These peptides also are candidate subunit antigens in compositions for antiserum production or vaccines. While the truncated sequences can be produced by various known treatments of native viral protein, it is generally preferred to make synthetic or recombinant peptides comprising HCV sequence. Peptides comprising these truncated HCV sequences can be made up entirely of HCV sequences (one or more epitopes, either contiguous or noncontiguous), or HCV sequences and heterologous sequences in a fusion protein. Useful

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heterologous sequences include sequences that provide for secretion from a recombinant host, enhance the immunological reactivity of the HCV epitope(s), or facilitate the coupling of the polypeptide to an immunoassay support or a vaccine carrier. See, E.G., EPO Pub. No. 116,201; U.S. Pat. No. 4,722,840; EPO Pub. No. 259,149; U.S. Pat. No. 4,629,783.

The size of peptides comprising the truncated HCV sequences can vary widely, the minimum size being a sequence of sufficient size to provide an HCV epitope, while the maximum size is not critical. For convenience, the maximum size usually is not substantially greater than that required to provide the desired HCV epitopes and function(s) of the heterologous sequence, if any. Typically, the truncated HCV amino acid sequence will range from about 5 to about 100 amino acids in length. More typically, however, the HCV sequence will be a maximum of about 50 amino acids in length, preferably a maximum of about 30 amino acids. It is usually desirable to select HCV sequences of at least about 10, 12 or 15 amino acids, up to a maximum of about 20 or 25 amino acids.

HCV amino acid sequences comprising epitopes can be identified in a number of ways. For example, the entire protein sequence corresponding to each of the NS5, envelope 1, and core regions can be screened by preparing a series of short peptides that together span

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the entire protein sequence of such regions. By starting with, for example, peptides of approximately 100 amino acids, it would be routine to test each peptide for the presence of epitope(s) showing a
5 desired reactivity, and then testing progressively smaller and overlapping fragments from an identified peptides of 100 amino acids to map the epitope of interest. Screening such peptides in an immunoassay is within the skill of the art. It is also known to carry
10 out a computer analysis of a protein sequence to identify potential epitopes, and then prepare peptides comprising the identified regions for screening.

The immunogenicity of the epitopes of HCV may also be enhanced by preparing them in mammalian or yeast
15 systems fused with or assembled with particle-forming proteins such as, for example, that associated with hepatitis B surface antigen. See, e.g., US 4,722,840. Constructs wherein the HCV epitope is linked directly to the particle-forming protein coding sequences
20 produce hybrids which are immunogenic with respect to the HCV epitope. In addition, all of the vectors prepared include epitopes specific to HBV, having various degrees of immunogenicity, such as, for example, the pre-S peptide. Thus, particles
25 constructed from particle forming protein which include HCV sequences are immunogenic with respect to HCV and HBV.

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Hepatitis surface antigen (HBSAg) has been shown to be formed and assembled into particles in S. cerevisiae (P. Valenzuela et al. (1982)), as well as in, for example, mammalian cells (P. Valenzuela et al. 5 1984)). The formation of such particles has been shown to enhance the immunogenicity of the monomer subunit. The constructs may also include the immunodominant epitope of HBSAg, comprising the 55 amino acids of the presurface (pre-S) region. Neurath et al. (1984). 10 Constructs of the pre-S-HBSAg particle expressible in yeast are disclosed in EPO 174,444, published March 19, 1986; hybrids including heterologous viral sequences for yeast expression are disclosed in EPO 175,261, published March 26, 1986. These constructs may also be 15 expressed in mammalian cells such as Chinese hamster ovary (CHO) cells using an SV40-dihydrofolate reductase vector (Michelle et al. (1984)).

In addition, portions of the particle-forming protein coding sequence may be replaced with codons 20 encoding an HCV epitope. In this replacement, regions which are not required to mediate the aggregation of the units to form immunogenic particles in yeast of mammals can be deleted, thus eliminating additional HBV antigenic sites from competition with the HCV epitope.

25

Vaccines

Vaccines may be prepared from one or more

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immunogenic peptides derived from HCV. The observed homology between HCV and Flaviviruses provides information concerning the peptides which are likely to be most effective as vaccines, as well as the regions of the genome in which they are encoded.

Multivalent vaccines against HCV may be comprised of one or more epitopes from one or more proteins derived from the NS5, envelope 1, and core regions. In particular, vaccines are contemplated comprising one or more HCV proteins or subunit antigens derived from the NS5, envelope 1, and core regions. The 5'UT region is not known to be translated.

The preparation of vaccines which contain an immunogenic peptide as an active ingredient, is known to one skilled in the art. Typically, such vaccines are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. The preparation may also be emulsified, or the protein encapsulated in liposomes. The active immunogenic ingredients are often mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the vaccine may contain minor amounts of auxiliary substances such as wetting or

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emulsifying agents, pH buffering agents, and/or adjuvants which enhance the effectiveness of the vaccine. Examples of adjuvants which may be effective include but are not limited to: aluminum hydroxide,

5 N-acetyl-muramyl-L-theronyl-D- isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl- D-isoglutamine (CGP 11637, referred to as nor-MDP), N- acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1- 2-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)- ethylamine (CGP

10 19835A, referred to as MTP-PE), and RIBI, which contains three components extracted from bacteria, monophosphoryl lipid A, trehalose dimycolate and cell wall skeleton (MPL+TDM+CWS) in a 2% squalene/Tween 80 emulsion. The effectiveness of an adjuvant may be

15 determined by measuring the amount of antibodies directed against an immunogenic peptide containing an HCV antigenic sequence resulting from administration of this peptide in vaccines which are also comprised of the various adjuvants.

20 The vaccines are conventionally administered parenterally, by injection, for example, either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, in some

25 cases, oral formulations. For suppositories, traditional binders and carriers may include, for example, polyalkylene glycols or triglycerides; such

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suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%. Oral formulations include such normally employed excipients as, for example,

- 5 pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

The examples below are provided for illustrative purposes and are not intended to limit the scope of the
10 present invention.

I. Detection of HCV RNA from Serum

RNA was extracted from serum using guanidinium salt, phenol and chloroform according to the
15 instructions of the kit manufacturer (RNAzol™ B kit, Cinna/Biotech). Extracted RNA was precipitated with isopropanol and washed with ethanol. A total of 25 µl serum was processed for RNA isolation, and the purified RNA was resuspended in 5 µl diethyl
20 pyrocarbonate treated water for subsequent cDNA synthesis.

II. cDNA Synthesis and Polymerase Chain Reaction (PCR) Amplification

25 Table 1 lists the sequence and position (with reference to HCV1) of all the PCR primers and probes used in these examples. Letter designations for

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nucleotides are consistent with 37 C.F.R. §§1.821-1.825. Thus, the letters A, C, G, T, and U are used in the ordinary sense of adenine, cytosine, guanine, thymine, and uracil. The letter M means A or C; R means A or G; W means A or T/U; S means C or G; Y means C or T/U; K means G or T/U; V means A or C or G, not T/U; H means A or C or T/U, not G; D means A or G or T/U, not C; B means C or G or T/U, not A; N means (A or C or G or T/U) or (unknown or other). Table 1 is set forth below:

Table 1

Seq. No.	Sequence (5'-3')	Nucleotide Position
	=====	=====
	67 CAAACGTAACACCAACCGRCGCCCCACAGG	374-402
15	68 ACAGAYCCGCAKAGRTCCCCCACG	1192-1169
	69 GCAACCTCGAGGTAGACGTCAGCCTATCCC	509-538
	70 GCAACCTCGTGGAAGGCGACAACCTATCCC	509-538
	71 GTCACCAATGATTGCCCTAACTCGAGTATT	948-977
	72 GTCACGAACGACTGCTCCAACCTCAAG	948-973
20	73 TGGACATGATCGCTGGWGCYCACTGGGG	1375-1402
	74 TGGAYATGGTGGYGGGGGCYCACTGGGG	1375-1402
	75 ATGATGAACTGGTCVCCYAC	1308-1327
	76 ACCTTVGCCCAGTTSCCCRCCATGGA	1453-1428
	77 AACCCACTCTATGYCCGGYCAT	205-226
25	78 GAATCGCTGGGGTGACCG	171-188
	79 CCATGAATCACTCCCCTGTGAGGAACTA	30-57
	80 TTGCGGGGGGCACGCCCAA	244-227

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For cDNA synthesis and PCR amplification, a protocol developed by Perkin-Elmer/Cetus (GeneAmp® RNA PCR kit) was used. Both random hexamer and primers with specific complementary sequences to HCV were employed to prime the reverse transcription (RT) reaction. All processes, except for adding and mixing reaction components, were performed in a thermal cycler (MJ Research, Inc.). The first strand cDNA synthesis reaction was inactivated at 99°C for 5 min, and then cooled at 50°C for 5 min before adding reaction components for subsequent amplification. After an initial 5 cycles of 97°C for 1 min, 50°C for 2 min, and 72°C for 3 min, 30 cycles of 94°C for 1 min, 55°C for 2 min, and 72°C for 3 min followed, and then a final 7 min of elongation at 72°C.

For the genotyping analysis, sequences 67 and 68 were used as primers in the PCR reaction. These primers amplify a segment corresponding to the core and envelope regions. After amplification, the reaction products were separated on an agarose gel and then transferred to a nylon membrane. The immobilized reaction products were allowed to hybridize with a ³²P-labelled nucleic acid corresponding to either Genotype I (core or envelope 1) or Genotype II (core or envelope 1). Nucleic acid corresponding to Genotype 1 comprised sequences numbered 69 (core), 71 (envelope), and 73 (envelope). Nucleic acid corresponding to

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Genotype II comprised sequences numbered 70 (core), 72 (envelope), and 74 (envelope).

5 The Genotype I probes only hybridized to the product amplified from isolates which had Genotype I sequence. Similarly, Genotype II probes only hybridized to the product amplified from isolates which had Genotype II sequence.

10 In another experiment, PCR products were generated using sequences 79 and 80. The products were analyzed as described above except Sequence No. 73 was used to detect Genotype I, Sequence No. 74 was used to detect Genotype II, Sequence No. 77 (5'UT) was used to detect Genotype III, and Sequence No. 78 (5'UT) was used to detect Genotype IV. Each sequence hybridized in a
15 genotype specific manner.

III. Detection of HCV GI-GIV using a sandwich hybridization assay for HCV RNA

20 An amplified solution phase nucleic acid sandwich hybridization assay format is described in this example. The assay format employs several nucleic acid probes to effect capture and detection. A capture probe nucleic acid is capable of associating a complementary probe bound to a solid support and HCV
25 nucleic acid to effect capture. A detection probe nucleic acid has a first segment (A) that binds to HCV nucleic acid and a second segment (B) that hybridizes to a second amplifier nucleic acid.

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The amplifier nucleic acid has a first segment (B*) that hybridizes to segment (B) of the probe nucleic acid and also comprises fifteen iterations of a segment (C). Segment C of the amplifier nucleic acid is

5 capable of hybridizing to three labeled nucleic acids.

Nucleic acid sequences which correspond to nucleotide sequences of the envelope 1 gene of Group I HCV isolates are set forth in sequences numbered 81-99. Table 2 sets forth the area of the HCV genome

10 to which the nucleic acid sequences correspond and a preferred use of the sequences.

Table 2

15	Probe Type	Sequence No.	Complement of Nucleotide Numbers
=====			
	Label	81	879-911
	Label	82	912-944
	Capture	83	945-977
20	Label	84	978-1010
	Label	85	1011-1043
	Label	86	1044-1076
	Label	87	1077-1109
	Capture	88	1110-1142
25	Label	89	1143-1175

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Table 2 continued

	Probe Type	Sequence No.	Complement of Nucleotide Numbers
5	=====		
	Label	90	1176-1208
	Label	91	1209-1241
	Label	92	1242-1274
	Capture	93	1275-1307
10	Label	94	1308-1340
	Label	95	1341-1373
	Label	96	1374-1406
	Label	97	1407-1439
	Capture	98	1440-1472
15	Label	99	1473-1505

Nucleic acid sequences which correspond to
 nucleotide sequences of the envelope 1 gene of Group II
 HCV isolates are set forth in sequences 100-118. Table
 20 3 sets forth the area of the HCV genome to which the
 nucleic acid corresponds and the preferred use of the
 sequences.

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Table 3

	Probe Type	Sequence No.	Complement of Nucleotide Numbers
5	=====		
	Label	100	879-911
	Label	101	912-944
	Capture	102	945-977
	Label	103	978-1010
10	Label	104	1011-1043
	Label	105	1044-1076
	Label	106	1077-1109
	Capture	107	1110-1142
	Label	108	1143-1175
15	Label	109	1176-1208
	Label	110	1209-1241
	Label	111	1242-1274
	Capture	112	1275-1307
	Label	113	1308-1340
20	Label	114	1341-1373
	Label	115	1374-1406
	Label	116	1407-1439
	Capture	117	1440-1472
	Label	118	1473-1505
25			

Nucleic acid sequences which correspond to
nucleotide sequences in the C gene and the 5'UT region

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are set forth in sequences 119-145. Table 4 identifies the sequence with a preferred use.

Table 4

5	Probe Type	Sequence No.
	=====	
	Capture	119
	Label	120
10	Label	121
	Label	122
	Capture	123
	Label	124
	Label	125
	Label	126
15	Capture	127
	Label	128
	Label	129
	Label	130
20	Capture	131
	Label	132
	Label	133
	Label	134
	Label	135
	Capture	136
25	Label	137
	Label	138

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Table 4 continued

	Probe Type	Sequence No.
	=====	
5	Label	139
	Capture	140
	Label	141
	Label	142
	Label	143
10	Capture	144
	Label	145

The detection and capture probe HCV-specific segments, and their respective names as used in this assay were as follows.

- 15 Capture sequences are sequences numbered 119-122 and 141-144.
 Detection sequences are sequences numbered 119-140.

20 Each detection sequence contained, in addition to the sequences substantially complementary to the HCV sequences, a 5' extension (B) which extension (B) is complementary to a segment of the second amplifier nucleic acid. The extension (B) sequence is identified in the Sequence Listing as Sequence No. 146, and is
 25 reproduced below.

AGGCATAGGACCCGTGTCTT

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Each capture sequence contained, in addition to the sequences substantially complementary to HCV sequences, a sequence complementary to DNA bound to a solid phase. The sequence complementary to DNA bound to a solid support was carried downstream from the capture sequence. The sequence complementary to the DNA bound to the support is set forth as Sequence No. 147 and is reproduced below.

CTTCTTTGGAGAAAGTGGTG

10 Microtiter plates were prepared as follows. White Microlite 1 Removawell strips (polystyrene microtiter plates, 96 wells/plate) were purchased from Dynatech Inc.

15 Each well was filled with 200 μ l 1 N HCl and incubated at room temperature for 15-20 min. The plates were then washed 4 times with 1X PBS and the wells aspirated to remove liquid. The wells were then filled with 200 μ l 1 N NaOH and incubated at room temperature for 15-20 min. The plates were again washed 4 times with 1X PBS and the wells aspirated to remove liquid.

25 Poly(phe-lys) was purchased from Sigma Chemicals, Inc. This polypeptide has a 1:1 molar ratio of phe:lys and an average m.w. of 47,900 gm/mole. It has an average length of 309 amino acids and contains 155 amines/mole. A 1 mg/ml solution of the polypeptide was mixed with 2M NaCl/1X PBS to a final concentration of

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0.1 mg/ml (pH 6.0). A volume of 200 μ l of this solution was added to each well. The plate was wrapped in plastic to prevent drying and incubated at 30°C overnight. The plate was then washed 4 times with 1X
5 PBS and the wells aspirated to remove liquid.

The following procedure was used to couple the nucleic acid, a complementary sequence to Sequence No. 147, to the plates, hereinafter referred to as immobilized nucleic acid. Synthesis of immobilized
10 nucleic acid having a sequence complementary to Sequence No. 133 was described in EPA 883096976. A quantity of 20 mg disuccinimidyl suberate was dissolved in 300 μ l dimethyl formamide (DMF). A quantity of 26
15 OD₂₆₀ units of immobilized nucleic acid was added to 100 μ l coupling buffer (50 mM sodium phosphate, pH 7.8). The coupling mixture was then added to the DSS-DMF solution and stirred with a magnetic stirrer for 30 min. An NAP-25 column was equilibrated with 10
20 mM sodium phosphate, pH 6.5. The coupling mixture DSS-DMF solution was added to 2 ml 10 mM sodium phosphate, pH 6.5, at 4°C. The mixture was vortexed to mix and loaded onto the equilibrated NAP-25 column. DSS-activated immobilized nucleic acid DNA was eluted from the column with 3.5 ml 10 mM sodium phosphate, pH
25 6.5. A quantity of 5.6 OD₂₆₀ units of eluted DSS-activated immobilized nucleic acid DNA was added to 1500 ml 50 mM sodium phosphate, pH 7.8. A volume of 50

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µl of this solution was added to each well and the plates were incubated overnight. The plate was then washed 4 times with 1X PBS and the wells aspirated to remove liquid.

- 5 Final stripping of plates was accomplished as follows. A volume of 200 µl of 0.2N NaOH containing 0.5% (w/v) SDS was added to each well. The plate was wrapped in plastic and incubated at 65°C for 60 min. The plate was then washed 4 times with 1X PBS and the
10 wells aspirated to remove liquid. The stripped plate was stored with desiccant beads at 2-8°C.

Serum samples to be assayed were analyzed using PCR followed by sequence analysis to determine the genotype.

- 15 Sample preparation consisted of delivering 50 µl of the serum sample and 150 µl P-K Buffer (2 mg/ml proteinase K in 53 mM Tris-HCl, pH 8.0/0.6 M NaCl/0.06 M sodium citrate/8 mM EDTA, pH 8.0/1.3%SDS/16µg/ml
20 sonicated salmon sperm DNA/7% formamide/50 fmoles capture probes/160 fmoles detection probes) to each well. Plates were agitated to mix the contents in the well, covered and incubated for 16 hr at 62°C.

- After a further 10 minute period at room temperature, the contents of each well were aspirated
25 to remove all fluid, and the wells washed 2X with washing buffer (0.1% SDS/0.015 M NaCl/ 0.0015 M sodium citrate). The amplifier nucleic acid was then added to

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each well (50 μ l of 0.7 fmole/ μ l solution in 0.48 M NaCl/0.048 M sodium citrate/0.1% SDS/0.5% "blocking reagent" (Boehringer Mannheim, catalog No. 1096 176)). After covering the plates and agitating to mix the contents in the wells, the plates were incubated for 30 min. at 52°C.

After a further 10 min period at room temperature, the wells were washed as described above.

Alkaline phosphatase label nucleic acid, disclosed in EP 883096976, was then added to each well (50 μ l/well of 2.66 fmoles/ μ l). After incubation at 52°C for 15 min., and 10 min. at room temperature, the wells were washed twice as above and then 3X with 0.015 M NaCl/0.0015 M sodium citrate.

An enzyme-triggered dioxetane (Schaap et al., Tet. Lett. (1987) 28:1159-1162 and EPA Pub. No. 0254051), obtained from Lumigen, Inc., was employed. A quantity of 50 μ l Lumiphos 530 (Lumigen) was added to each well. The wells were tapped lightly so that the reagent would fall to the bottom and gently swirled to distribute the reagent evenly over the bottom. The wells were covered and incubated at 37°C for 20-40 min.

Plates were then read on a Dynatech ML 1000 luminometer. Output was given as the full integral of the light produced during the reaction.

The assay positively detected each of the serum samples, regardless of genotype.

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IV. Expression of the Polypeptide Encoded in Sequences Defined by Differing Genotypes

HCV polypeptides encoded by a sequence within sequences 1-66 are expressed as a fusion polypeptide with superoxide dismutase (SOD). A cDNA carrying such sequences is subcloned into the expression vector pSODcfl (Steimer et al. 1986)).

First, DNA isolated from pSODcfl is treated with BamHI and EcoRI, and the following linker was ligated into the linear DNA created by the restriction enzymes:

5 GAT CCT GGA ATT CTG ATA AGA
CCT TAA GAC TAT TTT AA 3

After cloning, the plasmid containing the insert is isolated.

Plasmid containing the insert is restricted with EcoRI. The HCV cDNA is ligated into this EcoRI linearized plasmid DNA. The DNA mixture is used to transform E. coli strain D1210 (Sadler et al. (1980)). Polypeptides are isolated on gels.

20

V. Antigenicity of Polypeptides

The antigenicity of polypeptides formed in Section IV is evaluated in the following manner. Polyethylene pins arranged on a block in an 8 12 array (Coselco Mimetopes, Victoria, Australia) are prepared by placing the pins in a bath (20% v/v piperidine in dimethylformamide (DMF)) for 30 minutes at room

25

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temperature. The pins are removed, washed in DMF for 5 minutes, then washed in methanol four times (2 min/wash). The pins are allowed to air dry for at least 10 minutes, then washed a final time in DMF (5Min). 1-Hydroxybenzotriazole (HOBt, 367 mg) is dissolved in DMF (80 μ L) for use in coupling Fmoc-protected polypeptides prepared in Section IV.

The protected amino acids are placed in micro-titer plate wells with HOBt, and the pin block placed over the plate, immersing the pins in the wells. The assembly is then sealed in a plastic bag and allowed to react at 25°C for 18 hours to couple the first amino acids to the pins. The block is then removed, and the pins washed with DMF (2 min.), MeOH (4 x, 2 min.), and again with DMF (2 min.) to clean and deprotect the bound amino acids. The procedure is repeated for each additional amino acid coupled, until all octamers are prepared.

The free N-termini are then acetylated to compensate for the free amide, as most of the epitopes are not found at the N-terminus and thus would not have the associated positive charge. Acetylation is accomplished by filling the wells of a microtiter plate with DMF/acetic anhydride/triethylamine (5:2:1 v/v/v) and allowing the pins to react in the wells for 90 minutes at 20°C. The pins are then washed with DMF (2

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min.) and MeOH (4 x, 2 min.), and air dried for at least 10 minutes.

5 The side chain protecting groups are removed by treating the pins with trifluoroacetic acid/phenol/dithioethane (95:2.5:1.5, v/v/v) in polypropylene bags for 4 hours at room temperature. The pins are then washed in dichloromethane (2 x, 2 min.), 5% di-isopropylethylamine/dichloromethane (2 x, 5 min.), dichloromethane (5 min.), and air-dried for at least 10
10 minutes. The pins are then washed in water (2 min.), MeOH (18 hours), dried in vacuo, and stored in sealed plastic bags over silica gel. IV.B.15.b Assay of Peptides.

15 Octamer-bearing pins are treated by sonicating for 30 minutes in a disruption buffer (1% sodium dodecylsulfate, 0.1% 2-mercaptoethanol, 0.1 M NaH₂PO₄) at 60°C. The pins are then immersed several times in water (60°C), followed by boiling MeOH (2 min.), and allowed to air dry.

20 The pins are then precoated for 1 hour at 25°C in microtiter wells containing 200 µL blocking buffer (1% ovalbumin, 1% BSA, 0.1% Tween, and 0.05% NaN₃ in PBS), with agitation. The pins are then immersed in microtiter wells containing 175 µL antisera obtained
25 from human patients diagnosed as having HCV and allowed to incubate at 4°C overnight. The formation of a complex between polyclonal antibodies of the serum and

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the polypeptide initiates that the peptides give rise to an immune response in vivo. Such peptides are candidates for the development of vaccines.

Thus, this invention has been described and
5 illustrated. It will be apparent to those skilled in the art that many variations and modifications can be made without departing from the purview of the appended claims and without departing from the teaching and scope of the present invention.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

- 5 (i) APPLICANT: Tai-An Cha
- (ii) TITLE OF INVENTION: HCV GENOMIC SEQUENCES
 FOR DIAGNOSTICS AND THERAPEUTICS
- 10 (iii) NUMBER OF SEQUENCES: 147
- (iv) CORRESPONDENCE ADDRESS:
- (A) ADDRESSEE: Wolf, Greenfield & Sacks, P.C.
- (B) STREET: 600 Atlantic Avenue
- 15 (C) CITY: Boston
- (D) STATE: Massachusetts
- (E) COUNTRY: USA
- (F) ZIP: 02210
- 20 (v) COMPUTER READABLE FORM:
- (A) MEDIUM TYPE: Diskette, 5.25 inch
- (B) COMPUTER: IBM compatible
- (C) OPERATING SYSTEM: MS-DOS Version 3.3
- (D) SOFTWARE: WordPerfect 5.1

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- (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: Not Available
(B) FILING DATE: Not Available
(C) CLASSIFICATION: Not Available

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- (vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/697,326
(B) FILING DATE: 8 May 1991

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- (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Janiuk, Anthony J.
(B) REGISTRATION NUMBER: 29,809
(C) REFERENCE/DOCKET NUMBER: C0772/7000

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- (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (617) 720-3500
(B) TELEFAX: (617) 720-2441
(C) TELEX: EZEKIEL

- 20 (2) INFORMATION FOR SEQ ID NO: 1:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE: (ATCC # 40394)
(c) INDIVIDUAL ISOLATE: ns5hcv1

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1

CTCCACAGTC	ACTGAGAGCG	ACATCCGTAC	GGAGGAGGCA	40
ATCTACCAAT	GTTGTGACCT	CGACCCCCAA	GCCCGCGTGG	80
CCATCAAGTC	CCTCACCAG	AGGCTTTATG	TTGGGGGCCC	120
TCTTACCAAT	TCAAGGGGGG	AGAACTGCGG	CTATCGCAGG	160
TGCCGCGCGA	GCGGCGTACT	GACAACTAGC	TGTGGTAACA	200
CCCTCACTTG	CTACATCAAG	GCCCGGGCAG	CCTGTCGAGC	240
CGCAGGGCTC	CAGGACTGCA	CCATGCTCGT	GTGTGGCGAC	280
GACTTAGTCG	TTATCTGTGA	AAGCGCGGGG	GTCCAGGAGG	320
ACGCGGCGAG	CCTGAGAGCC			340

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(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

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(A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

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(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5i21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2

5	CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA	40
	ATTTACCAAT GTTGTGACCT GGACCCCCAA GCCCGCATGG	80
	CCATCAAGTC CCTCACTGAG AGGCTTTATG TCGGGGGCCC	120
	TCTTACCAAT TCAAGGGGGG AGAACTGCGG CTACCGCAGG	160
	TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTGGTAACA	200
10	CCCTCACTTG CTACATCAAG GCCCGGGCAG CCTGTGCGAGC	240
	CGCAGGGCTC CAGGACTGCA CCATGCTTGT GTGTGGCGAC	280
	GACTTAGTCG TTATCTGTGA AAGTGCGGGG GTCCAGGAGG	320
	ACGCGGCGAG CCTGAGAGCC	340

15 (2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 340 nucleotides
	(B) TYPE: nucleic acid
20	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) individual isolate: ns5pt1

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3

	CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA	40
	ATCTACCAAT GTTGTGATCT GGACCCCCAA GCCCGCGTGG	80
	CCATCAAGTC CCTCACTGAG AGGCTTTACG TTGGGGGGCCC	120
5	TCTTACCAAT TCAAGGGGGG AGAACTGCGG CTACCGCAGG	160
	TGCCGGGCGA GCGGCGTACT GACAACTAGC TGTGGTAATA	200
	CCCTCACTTG CTACATCAAG GCCCGGGCAG CCTGTCGAGC	240
	CGCAGGGCTC CGGGACTGCA CCATGCTCGT GTGTGGTGAC	280
	GACTTGGTCTG TTATCTGTGA GAGTGCGGGG GTCCAGGAGG	320
10	ACGCGGCGAG CCTGAGAGCC	340

(2) INFORMATION FOR SEQ ID NO: 4

(i) SEQUENCE CHARACTERISTICS:

15	(A) LENGTH: 340 nucleotides
	(B) TYPE: nucleic acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

20	(ii) MOLECULE TYPE: DNA
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(vi) ORIGINAL SOURCE:

	(C) INDIVIDUAL ISOLATE: ns5gm2
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25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4

	CTCTACAGTC ACTGAGAACG ACATCCGTAC GGAGGAGGCA	40
	ATTTACCAAT GTTGTGACCT GGACCCCCAA GCCCGCGTGG	80

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5 CCATCAAGTC CCTCACTGAG AGGCTTTATG TTGGGGGCCC 120
 CCTTACCAAT TCAAGGGGGG AAAACTGCGG CTATCGCAGG 160
 TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTGGTAACA 200
 CCCTCACTTG CTACATTAAG GCCCGGGCAG CCTGTCGAGC 240
 CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC 280
 GACTTAGTCG TTATCTGTGA GAGTGCGGGA GTCCAGGAGG 320
 ACGCGGCGAA CTTGAGAGCC 340

(2) INFORMATION FOR SEQ ID NO: 5

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

20 (C) INDIVIDUAL ISOLATE: ns5us17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5

25 CTCCACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA 40
 ATCTACCAAGT GTTGTGACCT GGACCCCCAA GCCCGCGTGG 80
 CCATCAAGTC CCTACCGAG AGGCTTTATG TCGGGGGCCC 120
 TCTTACCAAT TCAAGGGGGG AAAACTGCGG CTATCGCAGG 160
 TGCCGCGCAA GCGGCGTACT GACAACTAGC TGTGGTAACA 200

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CCCTCACTTG TTACATCAAG GCCCAAGCAG CCTGTCGAGC	240
CGCAGGGGCTC CGGGACTGCA CCATGCTCGT GTGTGGCGAC	280
GACTTAGTCG TTATCTGTGA AAGTCAGGGA GTCCAGGAGG	320
ATGCAGCGAA CCTGAGAGCC	340

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(2) INFORMATION FOR SEQ ID NO: 6

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5sp2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6

20	CTCTACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA	40
	ATCTACCAAT GTTGTGACCT GGACCCCGAA GCCCGTGTGG	80
	CCATCAAGTC CCTCACTGAG AGGCTTTATG TTGGGGGCCC	120
	TCTTACCAAT TCAAGGGGGG AGAACTGCGG CTACCGCAGG	160
	TGCCGCGCAA GCGGCGTACT GACGACTAGC TGTGGTAATA	200
25	CCCTCACTTG TTACATCAAG GCCCGGGCAG CCTGTCGAGC	240
	CGCAGGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC	280

GACCTAGTCG TTATCTGCGA AAGTGCGGGG GTCCAGGAGG 320
ACGCGGCGAG CCTGAGAGCC 340

(2) INFORMATION FOR SEQ ID NO: 7

5

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- 15 (C) INDIVIDUAL ISOLATE: ns5j1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7

CTCCACAGTC ACTGAGAATG ACACCCGTGT TGAGGAGTCA 40
ATTTACCAAT GTTGTGACTT GGCCCCGAA GCCAGACAGG 80
20 CCATAAGGTC GCTCACAGAG CGGCTCTATG TCGGGGGTCC 120
TATGACTAAC TCCAAAGGGC AGAACTGCGG CTATCGCCGG 160
TGCCGCGCGA GCGGCGTGCT GACGACTAGC TGCGGTAATA 200
CCCTCACATG CTACCTGAAG GCCACAGCGG CCTGTGAGC 240
TGCCAAGCTC CAGGACTGCA CGATGCTCGT GAACGGAGAC 280
25 GACCTTGTCG TTATCTGTGA AAGCGCGGGG AACCAAGAGG 320
ACGCGGCAAG CCTACGAGCC 340

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(2) INFORMATION FOR SEQ ID NO: 8

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(vi) ORIGINAL SOURCE:

- (C) INDIVIDUAL ISOLATE: ns5k1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8

15 CTCAACGGTC ACTGAGAATG ACATCCGTGT TGAGGAGTCA 40
 ATTTACCAA GTTGTGACTT GGCCCCCGAG GCCAGACAAG 80
 CCATAAGGTC GCTCACAGAG CGGCTTTACA TCGGGGGCCC 120
 CCTGACTAAT TCAAAAGGGC AGAACTGCGG CTATCGCCGA 160
 TGCCGCGCCA GCGGTGTGCT GACGACTAGC TGCGGTAATA 200
 20 CCCTCACATG TTACTTGAAG GCCACTGCGG CCTGTAGAGC 240
 TGCGAAGCTC CAGGACTGCA CGATGCTCGT GTGCGGAGAC 280
 GACCTTGTCG TTATCTGTGA AAGCGCGGGA ACCCAGGAGG 320
 ATGCGGCGAG CCTACGAGTC 340

25 (2) INFORMATION FOR SEQ ID NO: 9

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- (C) INDIVIDUAL ISOLATE: ns5k1.1

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9

	CTCAACGGTC ACCGAGAATG ACATCCGTGT TGAGGAGTCA	40
	ATTTATCAAT GTTGTGCCTT GGCCCCCGAG GCTAGACAGG	80
15	CCATAAGGTC GCTCACAGAG CGGCTTTATA TCGGGGGCCC	120
	CCTGACCAAT TCAAAGGGGC AGAACTGCGG TTATCGCCGG	160
	TGCCGCGCCA GCGGCGTACT GACGACCAGC TCGGGTAATA	200
	CCCTTACATG TTACTTGAAG GCCTCTGCAG CCTGTGAGC	240
	CGCGAAGCTC CAGGACTGCA CGATGCTCGT GTGTGGGGAC	280
20	GACCTTGTCG TTATCTGTGA AAGCGCGGGA ACCCAGGAGG	320
	ACGCGGCGAA CCTACGAGTC	340

(2) INFORMATION FOR SEQ ID NO: 10

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5gh6

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10

10	CTCAACGGTC ACTGAGAGTG ACATCCGTGT CGAGGAGTCG	40
	ATTTACCAAT GTTGTGACTT GGCCCCCGAA GCCAGGCAGG	80
	CCATAAGGTC GCTCACCGAG CGACTTTATA TCGGGGGCCC	120
	CCTGACTAAT TCAAAAGGGC AGAACTGCGG TTATCGCCGG	160
	TGCCGCGCGA GCGGCGTGCT GACGACTAGC TGCGGTAATA	200
15	CCCTCACATG TTACTTGAAG GCCTCTGCAG CCTGTGAGC	240
	TGCAAAGCTC CAGGACTGCA CGATGCTCGT GAACGGGGAC	280
	GACCTTGTCG TTATCTGCGA GAGCGCGGGA ACCCAAGAGG	320
	ACGCGGCGAG CCTACGAGTC	340

20 (2) INFORMATION FOR SEQ ID NO: 11

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 340 nucleotides

(B) TYPE: nucleic acid

25 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5spl

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11

	CTCCACAGTC	ACTGAGAGTG	ACATCCGTGT	TGAGGAGTCA	40
	ATTTACCAAT	GTTGTGACTT	GGCCCCCGAA	GCCAGACAGG	80
	CTATAAGGTC	GCTCACAGAG	CGGCTGTACA	TCGGGGGTCC	120
10	CCTGACTAAT	TCAAAAGGGC	AGAACTGCGG	CTATCGCCGG	160
	TGCCGCGCAA	GCGGCGTGCT	GACGACTAGC	TGCGGTAACA	200
	CCCTCACATG	TTACTTGAAG	GCCTCTGCGG	CCTGTGAGC	240
	TGCGAAGCTC	CAGGACTGCA	CGATGCTCGT	GTGCGGTGAC	280
	GACCTTGTCG	TTATCTGTGA	GAGCGCGGGA	ACCCAAGAGG	320
15	ACGCGGCGAG	CCTACGAGTC			340

(2) INFORMATION FOR SEQ ID NO: 12

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

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(C) individual isolate: ns5sp3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12

	CTCAACAGTC	ACTGAGAGTG	ACATCCGTGT	TGAGGAGTCA	40
5	ATCTACCAAT	GTTGTGACTT	GGCCCCCGAA	GCCAGACAGG	80
	CTATAAGGTC	GCTCACAGAG	CGGCTTTACA	TCGGGGGTCC	120
	CCTGACTAAT	TCAAAAGGGC	AGAACTGCGG	CTATCGCCGG	160
	TGCCGCGCAA	GCGGCGTGCT	GACGACTAGC	TGCGGTAATA	200
	CCCTCACATG	TTACCTGAAG	GCCAGTGCGG	CCTGTCGAGC	240
10	TGCGAAGCTC	CAGGACTGCA	CAATGCTCGT	GTGCGGTGAC	280
	GACCTTGTCG	TTATCTGTGA	GAGCGCGGGG	ACCCAAGAGG	320
	ACGCGGCGAG	CCTACGAGTC			340

(2) INFORMATION FOR SEQ ID NO: 13

15

(i) SEQUENCE CHARACTERISTICS:

	(A)	LENGTH: 340 nucleotides
	(B)	TYPE: nucleic acid
	(C)	STRANDEDNESS: single
20	(D)	TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

25	(C)	INDIVIDUAL ISOLATE: ns5k2
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13

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5 CTCAACCGTC ACTGAGAGAG ACATCAGAAC TGAGGAGTCC 40
 ATATACCGAG CCTGCTCCCT GCCTGAGGAG GCTCACATTG 80
 CCATACACTC GCTGACTGAG AGGCTCTACG TGGGAGGGCC 120
 CATGTTCAAC AGCAAGGGCC AGACCTGCGG GTACAGGCGT 160
 TGCCGCGCCA GCGGGGTGCT CACCACTAGC ATGGGGGAACA 200
 CCATCACATG CTATGTAAAA GCCCTAGCGG CTTGCAAGGC 240
 TGCAGGGATA GTTGCACCCT CAATGCTGGT ATGCGGCGAC 280
 GACTTAGTTG TCATCTCAGA AAGCCAGGGG ACTGAGGAGG 320
 ACGAGCGGAA CCTGAGAGCT 340

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(2) INFORMATION FOR SEQ ID NO: 14

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5arg8

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14

25 CTCTACAGTC ACGTAAAAGG ACATCACATC CTAGGAGTCC 40
 ATCTACCA GT CCTGTTC ACT GCCCGAGGAG GCTCGAACTG 80
 CTATACACTC ACTGACTGAG AGACTATACG TAGGGGGGCC 120

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CATGACAAAC AGCAAGGGCC AATCCTGCGG GTACAGGCGT 160
 TGCCGCGCGA GCGCAGTGCT CACCACCAGC ATGGGCAACA 200
 CACTCACGTG CTACGTAAAA GCCAGGGCGG CGTGTAACGC 240
 CGCGGGGATT GTTGCTCCCA CCATGCTGGT GTGCGGTGAC 280
 5 GACCTGGTCG TCATCTCAGA GAGTCAAGGG GCTGAGGAGG 320
 ACGAGCAGAA CCTGAGAGTC 340

(2) INFORMATION FOR SEQ ID NO: 15

10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 15 (ii) MOLECULE TYPE: DNA
 (vi) ORIGINAL SOURCE:
 (C) INDIVIDUAL ISOLATE: ns5i10
 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15
 CTCTACAGTC ACAGAGAGGG ACATCAGAAC CGAGGAGTCC 40
 ATCTATCTGT CCTGCTCACT GCCTGAGGAG GCCCGAACTG 80
 CTATACACTC ACTGACTGAG AGACTGTACG TAGGGGGGCC 120
 25 CATGACAAAC AGCAAGGGGC AATCCTGCGG GTACAGGCGT 160
 TGCCGCGCGA GCGGAGTGCT CACCACCAGC ATGGGCAACA 200
 CGCTCACGTG CTACGTGAAA GCCAGAGCGG CGTGTAACGC 240

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CGCGGGCATT GTTGCTCCCA CCATGTTGGT GTGCGGCGAC 280
GACCTGGTTG TCATCTCAGA GAGTCAGGGG GTCGAGGAAG 320
ATGAGCGGAA CCTGAGAGTC 340

5 (2) INFORMATION FOR SEQ ID NO: 16

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
(B) TYPE: nucleic acid
10 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5arg6

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16

CTCTACAGTC ACGGAGAGGG ACATCAGAAC CGAGGAGTCC 40
20 ATCTATCTGT CCTGTTCACT GCCTGAGGAG GCTCGAACTG 80
CCATACACTC ACTGACTGAG AGGCTGTACG TAGGGGGGCC 120
CATGACAAAC AGCAAAGGGC AATCCTGCGG GTACAGGCGT 160
TGCCGCGCGA GCGGAGTGCT CACCACCAGC ATGGGTAACA 200
CACTCACGTG CTACGTGAAA GCTAAAGCGG CATGTAACGC 240
25 CGCGGGCATT GTTGCCCCCA CCATGTTGGT GTGCGGCGAC 280
GACCTAGTCG TCATCTCAGA GAGTCAAGGG GTCGAGGAGG 320
ATGAGCGAAA CCTGAGAGCT 340

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(2) INFORMATION FOR SEQ ID NO: 17

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(vi) ORIGINAL SOURCE:

- (C) INDIVIDUAL ISOLATE: ns5k2b

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17

15 CTCAACCGTC ACGGAGAGGG ACATAAGAAC AGAAGAATCC 40
 ATATATCAGG GTTGTTCCCT GCCTCAGGAG GCTAGAACTG 80
 CTATCCACTC GCTCACTGAG AGACTCTACG TAGGAGGGCC 120
 CATGACAAAC AGCAAGGGAC AATCCTGCGG TTACAGGCGT 160
 TGCCGCGCCA GCGGGGTCTT CACCACCAGC ATGGGGAATA 200
 20 CCATGACATG CTACATCAAA GCCCTTGCAG CGTGCAAAGC 240
 TGCAGGGATC GTGGACCCTA TCATGCTGGT GTGTGGAGAC 280
 GACCTGGTCG TCATCTCGGA GAGCGAAGGT AACGAGGAGG 320
 ACGAGCGAAA CCTGAGAGCT 340

25 (2) INFORMATION FOR SEQ ID NO: 18

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5sa283

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18

CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCT	40
ATTTACCAAT CATTGTACTT GCAGCCTGAG GCGCGTGTGG	80
CAATACGGTC ACTCACCCAA CGCCTGTACT GTGGAGGCCC	120
CATGTATAAC AGCAAGGGGC AACAAATGTGG TTATCGTAGA	160
TGCCGCGCCA GCGGCGTCTT CACCACTAGT ATGGGCAACA	200
CCATGACGTG CTACATTAAG GCTTTAGCCT CCTGTAGAGC	240
CGCAAAGCTC CAGGACTGCA CGCTCCTGGT GTGTGGTGAT	320
GATAAAGCGA CCTGAGAGCC	340

20

(2) INFORMATION FOR SEQ ID NO: 19

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 340 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5sa156

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19

	CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCC	40
	ATTTACCAAT CATTGTACTT GCAGCCTGAG GCACGCGCGG	80
	CAATACGGTC ACTCACCCAA CGCCTGTACT GTGGAGGCCC	120
10	CATGTATAAC AGCAAGGGGC AACAAATGTGG TTACCGTAGA	160
	TGCCGCGCCA GCGGCGTCTT CACCACCAGT ATGGGCAACA	200
	CCATGACGTG CTACATCAAG GCTTCAGCCG CCTGTAGAGC	240
	TGCAAAGCTC CAGGACTGCA CGCTCCTGGT GTGTGGTGTG	280
	ACCTTGGTGG CCATTGCGA GAGCCAAGGG ACGCACGAGG	320
15	ATGAAGCGTG CCTGAGAGTC	340

(2) INFORMATION FOR SEQ ID NO: 20

(i) SEQUENCE CHARACTERISTICS:

20

(A) LENGTH: 340 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

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(C) INDIVIDUAL ISOLATE: ns5i11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20

	CTCTACTGTC	ACTGAACAGG	ACATCAGGGT	GGAAGAGGAG	40
5	ATATACCACT	GCTGTAACCT	TGAACCGGAG	GCCAGGAAAG	80
	TGATCTCCTC	CCTCACGGAG	CGGCTTTACT	GCGGGGGCCC	120
	TATGTTCAAC	AGCAAGGGGG	CCCAGTGTGG	TTATCGCCGT	160
	TGCCGTGCTA	GTGGAGTCCT	GCCTACCAGC	TTCGGCAACA	200
	CAATCACTTG	TTACATCAAG	GCTAGAGCGG	CTTCGAAGGC	240
10	CGCAGGCCTC	CGGAACCCGG	ACTTTCTTGT	CTGCGGAGAT	280
	GATCTGGTCG	TGGTGGCTGA	GAGTGATGGC	GTCGACGAGG	320
	ATAGAGCAGC	CCTGAGAGCC			340

(2) INFORMATION FOR SEQ ID NO: 21

15

(i) SEQUENCE CHARACTERISTICS:

	(A)	LENGTH: 340 nucleotides
	(B)	TYPE: nucleic acid
	(C)	STRANDEDNESS: single
20	(D)	TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

25	(C)	INDIVIDUAL ISOLATE: ns5i4
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21

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5 CTGACTGTC ACTGAACAGG ACATCAGGGT GGAAGAGGAG 40
 ATATACCAAT GCTGTAACCT TGAACCGGAG GCCAGGAAAG 80
 TGATCTCCTC CCTCACGGAG CGGCTTTACT GCGGGGGCCC 120
 TATGTTCAAT AGCAAGGGGG CCCAGTGTGG TTATCGCCGT 160
 TGCCGTGCTA GTGGAGTTCT GCCTACCAGC TTCGGCAACA 200
 CAATCACTTG TTACATCAAG GCTAGAGCGG CTGCGAAGGC 240
 CGCAGGGCTC CGGACCCCGG ACTTTCTCGT CTGCGGAGAT 280
 GATCTGGTTG TGGTGGCTGA GAGTGATGGC GTCGACGAGG 320
 ATAGAACAGC CCTGCGAGCC 340

10

(2) INFORMATION FOR SEQ ID NO: 22

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 340 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: ns5gh8

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22

25 CTCAACTGTC ACTGAACAGG ACATCAGGGT GGAAGAGGAG 40
 ATATACCAAT GCTGTAACCT TGAACCGGAG GCCAGGAAAG 80
 TGATCTCCTC CCTCACGGAA CGGCTTTACT GCGGGGGCCC 120

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5 TATGTTCAAC AGCAAGGGGG CCCAGTGTGG TTATCGCCGT 160
 TGCCGTGCCA GTGGAGTTCT GCCTACCAGC TTCGGCAACA 200
 CAATCACTTG TTACATCAA GCTAGAGCGG CTGCCGAAGC 240
 CGCAGGCCTC CGGAACCCGG ACTTTCTTGT CTGCGGAGAT 280
 GATCTGGTTG TGGTGGCTGA GAGTGATGGC GTCAATGAGG 320
 ATAGAGCAGC CCTGGGAGCC 340

(2) INFORMATION FOR SEQ ID NO: 23

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

- (vi) ORIGINAL SOURCE: (ATCC # 40394)
 (C) INDIVIDUAL ISOLATE: hcv1

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23

GACGGCGTTG GTAATGGCTC AGCTGCTCCG GATCCCACAA 40
 GCCATCTTGG ACATGATCGC TGGTGCTCAC TGGGGAGTCC 80
 TGGCGGGCAT AGCGTATTTC 100

25

(2) INFORMATION FOR SEQ ID NO: 24

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(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 100 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:
 10 (C) INDIVIDUAL ISOLATE: US5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24
 GACGGCGTTG GTGGTAGCTC AGGTACTCCG GATCCCACAA 40
 GCCATCATGG ACATGATCGC TGGAGCCCAC TGGGGAGTCC 80
 15 TGGCGGGCAT AGCGTATTTC 100

(2) INFORMATION FOR SEQ ID NO: 25

(i) SEQUENCE CHARACTERISTICS:
 20 (A) LENGTH: 100 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA
 25

(vi) ORIGINAL SOURCE:

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(C) INDIVIDUAL ISOLATE: AUS5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25
AACGGCGCTG GTAGTAGCTC AGCTGCTCAG GGTCCCGCAA 40
5 GCCATCGTGG ACATGATCGC TGGTGCCAC TGGGGAGTCC 80
TAGCGGGCAT AGCGTATTTT 100

(2) INFORMATION FOR SEQ ID NO: 26

10 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: US4

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26
GACAGCCCTA GTGGTATCGC AGTTACTCCG GATCCCACAA 40
GCCGTCATGG ATATGGTGGC GGGGGCCAC TGGGGAGTCC 80
TGGCGGGCCT TGCCTACTAT 100

25 (2) INFORMATION FOR SEQ ID NO: 27

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- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
5 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:
10 (C) INDIVIDUAL ISOLATE: ARG2
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27
AGCAGCCCTA GTGGTGTGCG AGTTACTCCG GATCCCACAA 40
AGCATCGTGG ACATGGTGGC GGGGGCCAC TGGGGAGTCC 80
15 TGGCGGGCCT TGCTTACTAT 100
- (2) INFORMATION FOR SEQ ID NO: 28
- (i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 100 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:

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(C) INDIVIDUAL ISOLATE: I15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28

	GGCAGCCCTA GTGGTGTGCG AGTTACTCCG GATCCCGCAA	40
5	GCTGTCGTGG ACATGGTGGC GGGGGCCAC TGGGGAATCC	80
	TAGCGGGTCT TGCCTACTAT	100

(2) INFORMATION FOR SEQ ID NO: 29

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: GH8

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29

	TGTGGGTATG GTGGTGGCGC ACGTCCTGCG TTTGCCCCAG	40
	ACCTTGTTTCG ACATAATAGC CGGGGCCCAT TGGGGCATCT	80
	TGGCGGGCTT GGCCTATTAC	100

25

(2) INFORMATION FOR SEQ ID NO: 30

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- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 100 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- 5 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:
- 10 (C) INDIVIDUAL ISOLATE: I4
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30
- TGTGGGTATG GTGGTAGCAC ACGTCCTGCG TCTGCCCCAG 40
- ACCTTGTTTCG ACATAATAGC CGGGGCCCAT TGGGGCATCT 80
- 15 TGGCAGGCCT AGCCTATTAC 100
- (2) INFORMATION FOR SEQ ID NO: 31
- (i) SEQUENCE CHARACTERISTICS:
- 20 (A) LENGTH: 100 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:

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(C) INDIVIDUAL ISOLATE: I11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31

5 TGTGGGTATG GTGGTGGCGC AAGTCCTGCG TTTGCCCCAG 40
 ACCTTGTTTCG ACGTGCTAGC CGGGGCCCAT TGGGGCATCT 80
 TGGCGGGCCT GGCCTATTAC 100

(2) INFORMATION FOR SEQ ID NO: 32

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: I10

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32

TACCACTATG CTCCTGGCAT ACTTGGTGCG CATCCCGGAG 40
 GTCATCCTGG ACATTATCAC GGGAGGACAC TGGGGCGTGA 80
 TGTTTGGCCT GGCTTATTTC 100

25

(2) INFORMATION FOR SEQ ID NO: 33

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(i). SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

- 10 (vi) ORIGINAL SOURCE: (ATCC # 40394)
(C) INDIVIDUAL ISOLATE: hcv1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33

15 GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC 40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC 120
GCTCAATGCC TGGAGATTG GGCCTGCCCC CGCAAGACTG 160
CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC 200
TGCCTGATAG GGTGCTTGCG AGTGCCCCCG GAGGTCTCGT 240
AGACCGTGCA CC 252

20

(2) INFORMATION FOR SEQ ID NO: 34

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: us5

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
GCTCAATGCC TGGAGATTG GCGTGCCCC CGCAAGACTG	160
CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA CC	252

10

15 (2) INFORMATION FOR SEQ ID NO: 35

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: aus1

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- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35
- | | | |
|---|---|-----|
| | GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC | 40 |
| | CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC | 80 |
| | GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC | 120 |
| 5 | GCTCAATGCC TGGAGATTG GGCACGCCCC CGCAAGATCA | 160 |
| | CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC | 200 |
| | TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT | 240 |
| | AGACCGTGCA CC | 252 |
- 10 (2) INFORMATION FOR SEQ ID NO: 36
- (i) SEQUENCE CHARACTERISTICS:
- | | |
|----|-----------------------------|
| | (A) LENGTH: 252 nucleotides |
| | (B) TYPE: nucleic acid |
| 15 | (C) STRANDEDNESS: single |
| | (D) TOPOLOGY: linear |
- (ii) MOLECULE TYPE: DNA
- 20 (vi) ORIGINAL SOURCE:
- (C) INDIVIDUAL ISOLATE: sp2
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36
- | | | |
|----|---|-----|
| | GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC | 40 |
| | CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC | 80 |
| 25 | GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATAAACCC | 120 |
| | GCTCAATGCC TGGAGATTG GCGTGCCCC CGCGAGACTG | 160 |

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CTAGCCGAGT AGTGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA CC	252

5 (2) INFORMATION FOR SEQ ID NO: 37

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
 (B) TYPE: nucleic acid
 10 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: gm2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
20 CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
GCTCAATGCC TGGAGATTG GCGTGCCCC CGCAAGACTG	160
CTAGCCGAGT AGTGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
25 AGACCGTGCA CC	252

(2) INFORMATION FOR SEQ ID NO: 38

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(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 252 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- 10 (C) INDIVIDUAL ISOLATE: i21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38

15 GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC 40
 CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80
 GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATAAACCC 120
 GCTCAATGCC TGGAGATTTG GGC GTGCCCC CGCAAGACTG 160
 CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC 200
 TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT 240
 AGACCGTGCA CC 252

20

(2) INFORMATION FOR SEQ ID NO: 39

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 252 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: us4

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC	40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
10 GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG	160
CTAGCCGAGT AGTGTGGGT GCGGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGC GAGGTCTCGT	240
AGACCGTGCA CC	252

15 (2) INFORMATION FOR SEQ ID NO: 40

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
20 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: jh1

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
5	GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG	160
	CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
	TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
	AGACCGTGCA TC	252

10 (2) INFORMATION FOR SEQ ID NO: 41

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 252 nucleotides
	(B) TYPE: nucleic acid
15	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (vi) ORIGINAL SOURCE:

	(C) INDIVIDUAL ISOLATE: nac5
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
25	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
	GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG	160

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CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA CC	252

5 (2) INFORMATION FOR SEQ ID NO: 42

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- 10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- 15 (C) INDIVIDUAL ISOLATE: arg2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
20 GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
GCTCAATGCC TGGAGATTG GCGTGCCCC CGCGAGACTG	160
CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA CC	252

25

(2) INFORMATION FOR SEQ ID NO: 43

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(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- 10 (C) INDIVIDUAL ISOLATE: spl

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43

15 GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC 40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC 120
GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG 160
CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC 200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT 240
AGACCGTGCA CC 252

20

(2) INFORMATION FOR SEQ ID NO: 44

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 252 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: gh1

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44

GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC	40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG	160
CTAGCCGAGT AGTGTTGGGT CCGGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA CC	252

10

15 (2) INFORMATION FOR SEQ ID NO: 45

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: i15

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45

	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC	120
5	GCTCAATGCC TGGAGATTG GCGGTGCCCC CGCGAGACTG	160
	CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
	TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
	AGACCGTGCA CC	252

10 (2) INFORMATION FOR SEQ ID NO: 46

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 252 nucleotides
	(B) TYPE: nucleic acid
15	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (vi) ORIGINAL SOURCE:

	(C) INDIVIDUAL ISOLATE: i10
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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46

	GCTAGTATCA GTGTCGTACA GCCTCCAGGC CCCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATTGCCG GGAAGACTGG GTCCTTTCTT GGATAAACCC	120
5	ACTCTATGCC CGGCCATTTG GCGGTGCCCC CGCAAGACTG	160
	CTAGCCGAGT AGCGTTGGGT TGCGAAAGGC CTTGTGGTAC	200
	TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
	AGACCGTGCA TC	252

10 (2) INFORMATION FOR SEQ ID NO: 47

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 252 nucleotides
	(B) TYPE: nucleic acid
15	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20 (vi) ORIGINAL SOURCE:

	(C) INDIVIDUAL ISOLATE: arg6
--	------------------------------

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47

	GTTAGTATGA GTCTCGTACA GCCTCCAGGC CCCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
25	GGAATTGCTG GGAAGACTGG GTCCTTTCTT GGATAAACCC	120
	ACTCTATGCC CAGCCATTTG GCGGTGCCCC CGCAAGACTG	160

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CTAGCCGAGT AGCGTTGGGT TCGGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
AGACCGTGCA TC	252

5 (2) INFORMATION FOR SEQ ID NO: 48

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 252 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- 10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- 15 (C) INDIVIDUAL ISOLATE: s21

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48

GTTAGTACGA GTGTCGTGCA GCCTCCAGGA CTCCCCCTCC	40
20 CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
GGAATCGCTG GGGTGACCGG GTCCTTTCTT GGAGCAACCC	120
GCTCAATACC CAGAAATTTG GCGGTGCCCC CGCGAGATCA	160
CTAGCCGAGT AGTGTGGGT GCGGAAAGGC CTTGTGGTAC	200
TGCCTGATAG GGTGCTTGCG AGTGCCCCGG GAGGTCTCGT	240
25 AGACCGTGCA AC	252

(2) INFORMATION FOR SEQ ID NO: 49

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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 252 nucleotides

(B) TYPE: nucleic acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: gj61329

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49

15	GTTAGTACGA GTGTCGTGCA GCCTCCAGGA CCCCCCTCC	40
	CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC	80
	GGAATCGCTG-GGGTGACCGG GTCCTTTCTT GGAGTAACCC	120
	GCTCAATACC CAGAAATTTG GCGGTGCCCC CGCGAGATCA	160
	CTAGCCGAGT AGTGTTGGGT CGCGAAAGGC CTTGTGGTAC	200
20	TGCCTGATAG GGTGCTTGCG AGTGCCCCCG GAGGTCTCGT	240
	AGACCGTGCA AC	252

(2) INFORMATION FOR SEQ ID NO: 50

25 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 180 nucleotides

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: DNA
(vi) ORIGINAL SOURCE:
(C) INDIVIDUAL ISOLATE: sa3

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50

10
GTTAGTATGA GTGTCGAACA GCCTCCAGGA CCCCCCCTCC 40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80
GGAATTGCCG GGATGACCGG GTCCTTTCTT GGATAAACCC 120
GCTCAATGCC CGGAGATTTG GCGTGCCCC CGCGAGACTG 160
15 CTAGCCGAGT AGTGTTGGGT 180

(2) INFORMATION FOR SEQ ID NO: 51

(i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 180 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

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(C) INDIVIDUAL ISOLATE: sa4

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51

5 GTTAGTATGA GTGTCGAACA GCCTCCAGGA CCCCCCTCC 40
CGGGAGAGCC ATAGTGGTCT GCGGAACCGG TGAGTACACC 80

GGAATTGCCG GGATGACCGG GTCCTTTCTT GGATAAACCC 120
GCTCAATGCC CGGAGATTG GCGTGCCCC CGCGAGACTG 160
CTAGCCGAGT AGTGTTGGGT 180

10

(2) INFORMATION FOR SEQ ID NO: 52

(i) SEQUENCE CHARACTERISTICS:

15 (A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(vi) ORIGINAL SOURCE: (ATCC # 40394)

(C) INDIVIDUAL ISOLATE: hcv1

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52

	ATGAGCACGA ATCCTAAACC TCAAAAAAAAA AACAAACGTA	40
	ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
5	GGCCCTAGAT TGGGTGTGCG CGCGACGAGA AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCCAA	200
	GGCTCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGC TCGGGGTGGG	280
	CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGCTG	320
10	GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT ACCGCTCGTC GCGCCCCCTC TTGGAGGCGC	440
	TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
	GGCGTGA ACT ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
15	TCTCTATCTT CTTCTGGCC CTGCTCTCT	549

(2) INFORMATION FOR SEQ ID NO: 53

- (i) SEQUENCE CHARACTERISTICS:
- 20 (A) LENGTH: 549 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:

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(C) INDIVIDUAL ISOLATE: us5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53

	ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
5	ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
	GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCCAA	200
	GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG	240
10	TACCCTTGGC CCCTCTATGG CAATGAGGGT TGCGGGTGGG	280
	CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGTTG	320
	GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCACA	400
	TGGGGTACAT ACCGCTCGTC GCGCCCCCTC TTGGAGGCGC	440
15	TGCCAGGGCT CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
	GGCGTGAACT ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
	TCTCTATCTT CCTTCTGGCC CTGCTCTCT	549

(2) INFORMATION FOR SEQ ID NO: 54

20

(i) SEQUENCE CHARACTERISTICS:

- | | |
|----|-----------------------------|
| | (A) LENGTH: 549 nucleotides |
| | (B) TYPE: nucleic acid |
| | (C) STRANDEDNESS: single |
| 25 | (D) TOPOLOGY: linear |

(ii) MOLECULE TYPE: DNA

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(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: aus1

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54
 ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG TCGCCCACAG GACGTTAAGT TCCCGGGTGG 80
 CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG 120
 GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG 160
 10 AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCTAA 200
 GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG 240
 TACCCCTGGC CCCTCTATGG TAATGAGGGT TGC GGATGGG 280
 CGGGATGGCT CCTGTCCCCC CGTGGCTCTC GGCCTAGTTG 320
 GGGCCCTACA GACCCCGGC GTAGGTCGCG CAATTTGGGT 360
 15 AAGGTCATCG ATACCCTCAC GTGCGGCTTC GCCGACCACA 400
 TGGGGTACAT TCCGCTCGTT GGCGCCCTC TTGGGGGCGC 440
 TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC 480
 GCGTGAACT ATGCAACAGG GAATCTTCCT GGTGCTCTT 520
 TCTCTATCTT CCTTCTGGCC CTTCTCTCT 549

20

(2) INFORMATION FOR SEQ ID NO: 55

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides
 25 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: sp2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55

	ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
	ACACCAACCG TCGCCCACAG GACGTCAAGT TCCCGGGTGG	80
10	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
	GGCCCTAGAT TGGGTGTGCG CACGACGAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CCATCCCCAA	200
	GGCTCGTCGA CCCGAGGGCA GGACCTGGGC TCAGCCCGGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGC TGCGGGTGGG	280
15	CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGCTG	320
	GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT ACCGCTCGTC GGCGCCCCTC TTGGAGGCGC	440
	TGCCAGAGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
20	GGCGTGA ACT ATGCAACAGG GAACCTTCCC GGTTGCTCTT	520
	TCTCTATCTT CCTTCTGGCC CTGCTCTCT	549

(2) INFORMATION FOR SEQ ID NO: 56

25 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

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~~(C) STRANDEDNESS: single~~

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: gm2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56

10	ATGAGCACGA ATCCTAAACC TCAAAGAAGA ACCAAACGTA	40
	ACACCAACCG TCGCCCACAG GACGTCAAGT TCCCGGGTGG	80
	CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
	GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGAGGT AGACGTCAGC CTATCCCCAA	200
15	GGCACGTCGG CCCGAGGGTA GGACCTGGGC TCAGCCCGGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGT TGCGGGTGGG	280
	CGGGATGGCT CCTGTCTCCC CGCGGCTCTC GGCCTAACTG	320
	GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTTGGGT	360
	AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
20	TGGGGTACAT ACCGCTCGTC GCGCCCCCTC TTGGAGGCGC	440
	TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
	GGCGTGAAC ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
	TCTCTATCTT CCTTCTGGCC CTGCTCTCT	549

25 (2) INFORMATION FOR SEQ ID NO: 57

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 549 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

- (ii) MOLECULE TYPE: DNA
- (vi) ORIGINAL SOURCE:
- (C) INDIVIDUAL ISOLATE: i21

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57

ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGTGG	80
CGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG	120
GGCCCTAGAT TGGGTGTGCG CGCGACGAGG AAGACTTCCG	160
15 AGCGGTCGCA ACCTCGTGGT AGACGCCAGC CTATCCCCAA	200
GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCCGGG	240
TACCCTTGGC CCCTCTATGG CAATGAGGGT TCGGGGTGGG	280
CGGGATGGCT CCTGTCTCCC CGTGGCTCTC GGCCTAGCTG	320
GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTTGGGT	360
20 AAGGTCATCG ATACCCTTAC GTGCGGCTTC GCCGACCTCA	400
TGGGGTACAT ACCGCTCGTC GGCGCCCCCTC TTGGAGGCGC	440
TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC	480
GGCGTGA ACT ATGCAACAGG GAACCTTCCT GGTGCTCTT	520
TTTCTATTTT CCTTCTGGCC CTGCTCTCT	549

25

- (2) INFORMATION FOR SEQ ID NO: 58

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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

5 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

10 (C) INDIVIDUAL ISOLATE: us4

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58

	ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
	ACACCAACCG CCGCCCACAG GACGTTAAGT TCCCGGGCGG	80
15	TGGCCAGGTC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG	120
	GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA	200
	GGCTCGCCAG CCCGAGGGCA GGGCCTGGGC TCAGCCCGGG	240
	TACCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG	280
20	CAGGATGGCT CCTGTCACCC CGTGGCTCTC GGCCTAGTTG	320
	GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTGGGT	360
	AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT TCCGCTCGTC GCGCCCCCCC TTAGGGGCGC	440
	TGCCAGGGCC TTGGCGCATG GCGTCCGGGT TCTGGAGGAC	480
25	GGCGTGA ACT ACGCAACAGG GAATCTGCCC GGTGCTCCT	520
	TTTCTATCTT CCTCTGGCT CTGCTGTCC	549

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(2) INFORMATION FOR SEQ ID NO: 59

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 549 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: jh1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59

15 ATGAGCACAA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
ACACCAACCG CCGCCCACAG GACGTCAAGT TCCCGGGCGG 80
TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG 120
GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG 160
AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA 200
20 GGCTCGCCAG CCCGAGGGCA GGGCCTGGGC TCAGCCCGGG 240
TACCCTTGGC CCCTCTATGG CAACGAGGGT ATGGGGTGGG 280
CAGGATGGCT CCTGTCACCC CGTGGCTCTC GGCCTAGTTG 320
GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTTGGGT 360
AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA 400
25 TGGGGTACAT TCCGCTTGTC GGC GCCCCCCC TAGGGGGCGC 440
TGCCAGGGCC CTGGCACATG GTGTCCGGGT TCTGGAGGAC 480
GGCGTGA ACT ATGCAACAGG GAATTTGCC GGTGCTCTT 520

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TCTCTATCTT CCTCTTGGCT CTGCTGTCC

549

(2) INFORMATION FOR SEQ ID NO: 60

5 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: nac5

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60

ATGAGCACAA ATCCTAAACC CCAAAGAAAA ACCAAACGTA	40
ACACCAACCG TCGCCACAG GACGTCAAGT TCCCGGGCGG	80
TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG	120
20 GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG	160
AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA	200
GGCTCGCCGG CCCGAGGGCA GGTCTGGGC TCAGCCCGGG	240
TACCCTTGGC CCCTCTATGG CAACGAGGGT ATGGGGTGGG	280
CAGGATGGCT CCTGTCACCC CGCGGCTCCC GGCCTAGTTG	320
25 GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTGGGT	360
AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA	400

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TGGGGTACAT TCCGCTCGTC GGCGCCCCC TAGGGGGCGC 440
 TGCCAGGGCC CTGGCACATG GTGTCCGGGT TCTGGAGGAC 480
 GGCGTGAAC ATGCAACAGG GAATTTGCCT GGTGCTCTT 520
 TCTCTATCTT CCTCTTGGCT CTGCTGTCC 549

5

(2) INFORMATION FOR SEQ ID NO: 61

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 549 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

15

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: arg2

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61

ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG CCGCCACAG GACGTCAAGT TCCGGGGCGG 80
 TGGTCAGATC GTTGGTGGAG TTTACTTGTT GCCGCGCAGG 120
 GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG 160
 AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA 200
 GGCTCGCCAG CCCGAGGGTA GGGCCTGGGC TCAGCCCGGG 240
 TACCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG 280
 CAGGGTGGCT CCTGTCCCC CGCGGCTCCC GGCCTAGTTG 320

25

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	GGGCCCCACA GACCCCCGGC GTAGGTCGCG TAATTTGGGT	360
	AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT TCCGCTCGTC GGC GCCCCCC TAGGGGGCGC	440
	TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAGGAC	480
5	GGCGTGAACT ATGCAACAGG GAATCTGCCC GGTGCTCTT	520
	TCTCTATCTT CCTCTTGGCT TTGCTGTCC	549

(2) INFORMATION FOR SEQ ID NO: 62

(i) SEQUENCE CHARACTERISTICS:

10	(A) LENGTH: 549 nucleotides
	(B) TYPE: nucleic acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

15	(ii) MOLECULE TYPE: DNA
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(vi) ORIGINAL SOURCE:

	(C) INDIVIDUAL ISOLATE: spl
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20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62

	ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA	40
	ACACCAACCG CCGCCACAG GACGTCAAGT TCCCGGGCGG	80
	TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG	120
	GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG	160
25	AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA	200
	GGCTCGCCGG CCCGAGGGCA GGGCCTGGGC TCAGCCCGGG	240
	TATCCTTGGC CCCTCTATGG CAATGAGGGT CTGGGGTGGG	280

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	CAGGATGGCT	CCTGTCACCC	CGCGGCTCTC	GGCCTAGCTG	320
	GGGCCCTACC	GACCCCCGGC	GTAGGTCGCG	CAACTTGGGT	360
	AAGGTCATCG	ATACCCTTAC	GTGCGGCTTC	GCCGACCTCA	400
	TGGGGTACAT	TCCGCTCGTC	GGCGCCCCCC	TTAGGGGCGC	440
5	TGCCAGGGCC	CTGGCGCATG	GCGTCCGGGT	TCTGGAGGAC	480
	GGCGTGAAC	ATGCAACAGG	GAATTTGCCC	GGTTGCTCTT	520
	TCTCTATCTT	CCTCTTGGCT	TTGCTGTCC		549

(2) INFORMATION FOR SEQ ID NO: 63

10

(i) SEQUENCE CHARACTERISTICS:

- | | | |
|----|-----|-------------------------|
| | (A) | LENGTH: 549 nucleotides |
| | (B) | TYPE: nucleic acid |
| | (C) | STRANDEDNESS: single |
| 15 | (D) | TOPOLOGY: linear |

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

- | | | |
|----|-----|-------------------------|
| 20 | (C) | INDIVIDUAL ISOLATE: ghl |
|----|-----|-------------------------|

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63

	ATGAGCACGA	ATCCTAAACC	TCAAAGAAAA	ACCAAACGTA	40
	ACACCAACCG	CCGCCCACAG	GACGTCAAGT	TCCCGGGCGG	80
25	TGGTCAGATC	GTTGGTGGAG	TTTACTTGTT	GCCGCGCAGG	120
	GGCCCCAGGT	TGGGTGTGCG	CGCGACTAGG	AAGACTTCCG	160
	AGCGGTCGCA	ACCTCGTGGA	AGGCGACAAC	CTATCCCCAA	200

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5 GGCTCGCCGG -CCCGAGGGCA- GGGCCTGGGC TCAGCCCGGG 240
 TACCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG 280
 CAGGATGGCT CCTGTCACCC CGTGGTTCTC GGCCTAGTTG 320
 GGGCCCCACG GACCCCCGGC GTAGGTCGCG CAATTTGGGT 360
 AAGATCATCG ATACCCTCAC GTGCGGCTTC GCCGACCTCA 400
 TGGGGTACAT TCCGCTCGTC GGC GCCCCCCC TAGGGGGCGC 440
 TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAGGAC 480
 GGC GTGA ACT ATGCAACAGG GAATCTGCCC GGT TGCTCCT 520
 TTTCTATCTT CCTTCTGGCT TTGCTGTCC 549

10

(2) INFORMATION FOR SEQ ID NO: 64

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 549 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: i15

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64

ATGAGCACGA ATCCTAAACC TCAAAGAAAA ACCAAACGTA 40
 ACACCAACCG CCGCCACAG GACGTCAAGT TCCCGGGCGG 80
 TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG 120

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	GGCCCCAGGT TGGGTGTGCG CGCGACTAGG AAGACTTCCG	160
	AGCGGTCGCA ACCTCGTGGA AGGCGACAAC CTATCCCCAA	200
	GGCTCGCCAG CCCGAGGGCA GGGCCTGGGC TCAGCCCCGGG	240
	TACCCCTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG	280
5	CAGGATGGCT CCTGTCACCC CGCGGCTCCC GGCCTAGTTG	320
	GGGCCCCAAA GACCCCCGGC GTAGGTCGCG TAATTTGGGT	360
	AAGGTCATCG ATACCCTCAC ATGCGGCTTC GCCGACCTCA	400
	TGGGGTACAT TCCGCTCGTC GGCGCCCCCT TAGGGGGCGC	440
	TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAGGAC	480
10	GGCGTGA ACT ATGCAACAGG GAATCTACCC GGTGCTCTT	520
	TCTCTATCTT CCTCTTGGCT TTGCTGTCC	549

(2) INFORMATION FOR SEQ ID NO: 65

15 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 549 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

(vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: i10

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65

ATGAGCACAA ATCCTAAACC TCAAAGAAAA ACCAAAAGAA 40

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	ACACTAACCG	CCGCCCACAG	GACGTCAAGT	TCCCGGGCGG	80
	TGGCCAGATC	GTTGGCGGAG	TATACTTGCT	GCCGCGCAGG	120
	GGCCCGAGAT	TGGGTGTGCG	CGCGACGAGG	AAAACCTCCG	160
	AACGATCCCA	GCCACGCGGA	AGGCGTCAGC	CCATCCCTAA	200
5	AGATCGTCGC	ACCGCTGGCA	AGTCCTGGGG	AAGGCCAGGA	240
	TATCCTTGGC	CCCTGTATGG	GAATGAGGGT	CTCGGCTGGG	280
	CAGGGTGGCT	CCTGTCCCCC	CGTGGCTCTC	GCCCTTCATG	320
	GGGCCCCACT	GACCCCCGGC	ATAGATCGCG	CAACTTGGGT	360
	AAGGTCATCG	ATACCCTAAC	GTGCGGTTTT	GCCGACCTCA	400
10	TGGGGTACAT	TCCCGTCATC	GGCGCCCCCG	TTGGAGGCGT	440
	TGCCAGAGCT	CTCGCCACAG	GAGTGAGGGT	TCTGGAGGAT	480
	GGGGTAAATT	ATGCAACAGG	GAATTGCCC	GGTTGCTCTT	520
	TCTCTATCTT	TCTCTTAGCC	CTCTTGTCT		549

15 (2) INFORMATION FOR SEQ ID NO: 66

(i) SEQUENCE CHARACTERISTICS:

	(A)	LENGTH: 510 nucleotides
	(B)	TYPE: nucleic acid
20	(C)	STRANDEDNESS: single
	(D)	TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (vi) ORIGINAL SOURCE:

(C) INDIVIDUAL ISOLATE: arg6

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66

	ATGAGCACAA ATCCTCAACC TCAAAGAAAA ACCAAAAGAA	40
	ACACTAACCG CCGCCACAG GACGTCAAGT TCCCGGGCGG	80
	TGGTCAGATC GTTGGCGGAG TATACTTGTT GCCGCGCAGG	120
5	GGCCCCAGGT TGGGTGTGCG CGCGACGAGG AAAACTTCCG	160
	AACGGTCCCA GCCACGTGGG AGGCGCCAGC CCATCCCCAA	200
	AGATCGGCGC ACCACTGGCA AGTCCTGGGG GAAGCCAGGA	240
	TACCCTTGGC CCCTGTATGG GAATGAGGGT CTCGGCTGGG	280
	CAGGGTGGCT CCTGTCCCCC CGCGGTTCTC GCCCTTCATG	320
10	GGGCCCCACT GACCCCCGGC ATAGATCACG CAACTTGGGT	360
	AAGGTCATCG ATACCCTAAC GTGTGGTTTT GCCGACCTCA	400
	TGGGGTACAT TCCCGTCGGT GGTGCCCCCG TTGGTGGTGT	440
	CGCCAGAGCC CTTGCCCATG GGGTGAGGGT TCTGGAAGAC	480
	GGGATAAATT ATGCAACAGG GAATCTGCCC	510

15

(2) INFORMATION FOR SEQ ID NO: 67

(i) SEQUENCE CHARACTERISTICS:

	(A) LENGTH: 29 nucleotides
20	(B) TYPE: nucleic acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67

CAAACGTAAC ACCAACCGRC GCCCACAGG	29
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(2) INFORMATION FOR SEQ ID NO: 68

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 24 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68

ACAGAYCCGC AKAGRTC CCC CACG

24

15 (2) INFORMATION FOR SEQ ID NO: 69

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 30 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69

CGAACCTCGA GGTAGACGTC AGCCTATCCC

30

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(2) INFORMATION FOR SEQ ID NO: 70

(i) SEQUENCE CHARACTERISTICS:

5

- (A) LENGTH: 30 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70

GCAACCTCGT GGAAGGCGAC AACCTATCCC

30

(2) INFORMATION FOR SEQ ID NO: 71

15

(i) SEQUENCE CHARACTERISTICS:

20

- (A) LENGTH: 30 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71

25

GTCACCAATG ATTGCCCTAA CTCGAGTATT

30

(2) INFORMATION FOR SEQ ID NO: 72

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- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72
GTCACGAACG ACTGCTCCAA CTCAAG 26
- (2) INFORMATION FOR SEQ ID NO: 73
- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73
TGGACATGAT CGCTGGWGCY CACTGGGG 28
- 25 (2) INFORMATION FOR SEQ ID NO: 74

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- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 28 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: DNA
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74
 TGGAYATGGT GGYGGGGGCY CACTGGGG 28
- (2) INFORMATION FOR SEQ ID NO: 75
- 15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 nucleotides
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75
 ATGATGAACT GGTCVCCYAC 20
- 25 (2) INFORMATION FOR SEQ ID NO: 76
- (i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 26 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 5 (ii) MOLECULE TYPE: DNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76
ACCTTVGCCC AGTTSCCCRC CATGGA 26
- 10 (2) INFORMATION FOR SEQ ID NO: 77
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 nucleotides
(B) TYPE: nucleic acid
15 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77
AACCCACTCT ATGYCCGGYC AT 22
- (2) INFORMATION FOR SEQ ID NO: 78
- 25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 nucleotides
(B) TYPE: nucleic acid

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(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78

GAATCGCTGG GGTGACCG

18

(2) INFORMATION FOR SEQ ID NO: 79

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75

20

CCATGAATCA CTCCCCTGTG AGGAACTA

28

(2) INFORMATION FOR SEQ ID NO: 80

(i) SEQUENCE CHARACTERISTICS:

25

(A) LENGTH: 18 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80
TTGCGGGGGC ACGCCCAA 18

(2) INFORMATION FOR SEQ ID NO: 81

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81
YGAAGCGGGC ACAGTCARRC AAGARAGCAG GGC 33

20

(2) INFORMATION FOR SEQ ID NO: 82

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82
RTARAGCCCY GWGGAGTTGC GCACTTGGTR GGC 33

(2) INFORMATION FOR SEQ ID NO: 83

(i) SEQUENCE CHARACTERISTICS:
10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83
RATACTCGAG TTAGGGCAAT CATTGGTGAC RTG 33

20 (2) INFORMATION FOR SEQ ID NO: 84

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
25 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84
AGYRTGCAGG ATGGYATCRK BCGYCTCGTA CAC

33

5

(2) INFORMATION FOR SEQ ID NO: 85

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85
GTTRCCCTCR CGAACGCAAG GGACRCACCC CGG

33

(2) INFORMATION FOR SEQ ID NO: 86

20 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86
CGTRGGGGTY AYC GCCACCC AACACCTCGA GRC

33

(2) INFORMATION FOR SEQ ID NO: 87

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87
CGTYGYGGGG AGTTTGCCRT CCCTGGTGGC YAC

15

33

(2) INFORMATION FOR SEQ ID NO: 88

(i) SEQUENCE CHARACTERISTICS:

20

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88

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CCCGACAAGC AGATCGATGT GACGTCGAAG CTG

33

(2) INFORMATION FOR SEQ ID NO: 89

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10

- (ii) MOLECULE TYPE: DNA

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89

CCCCACGTAG ARGGCCGARC AGAGRGTGGC GCY

33

15

(2) INFORMATION FOR SEQ ID NO: 90

- 20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

- (ii) MOLECULE TYPE: DNA

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90

YTGRCCGACA AGAAAGACAG ACCCGCAYAR GTC

33

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(2) INFORMATION FOR SEQ ID NO: 91

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91

CGTCCAGTGG YGCCTGGGAG AGAAGGTGAA CAG

33

15 (2) INFORMATION FOR SEQ ID NO: 92

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92

GCCGGGATAG ATRGARCAAT TGCARYCTTG CGT

33

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(2) INFORMATION FOR SEQ ID NO: 93

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93

CATATCCCAT GCCATGCGGT GACCCGTTAY ATG

33

(2) INFORMATION FOR SEQ ID NO: 94

15

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94

25

YACCAAYGCC GTCGTAGGGG ACCARTTCAT CAT

33

(2) INFORMATION FOR SEQ ID NO: 95

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- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
5 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95
10 GATGGCTTGT GGGATCCGGA GYASCTGAGC YAY 33
- (2) INFORMATION FOR SEQ ID NO: 96
- (i) SEQUENCE CHARACTERISTICS:
15 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96
GACTCCCCAG TGRGCWCCAG CGATCATRTC CAW 33
- 25 (2) INFORMATION FOR SEQ ID NO: 97
- (i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

- (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97
CCCCACCATG GAGAAATACG CTATGCCCGC YAG 33

10 (2) INFORMATION FOR SEQ ID NO: 98

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - 15 (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: DNA

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98
TAGYAGCAGY ACTACYARGA CCTTCGCCCA GTT 33

(2) INFORMATION FOR SEQ ID NO: 99

- 25 (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99

GSTGACGTGR GTKTCYGCGT CRACGCCGGC RAA

33

(2) INFORMATION FOR SEQ ID NO: 100

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100

20

GGAAGYTGGG ATGGTYARRC ARGASAGCAR AGC

33

(2) INFORMATION FOR SEQ ID NO: 101

(i) SEQUENCE CHARACTERISTICS:

25

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101
GTAYAYYCCG GACRCGTTGC GCACTTCRTA AGC 33

(2) INFORMATION FOR SEQ ID NO: 102

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102
AATRCTTGMG TTGGAGCART CGTTYGTGAC ATG 33

20 (2) INFORMATION FOR SEQ ID NO: 103

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103

RGYRTGCATG ATCAYGTCCG YYGCCTCATA CAC

33

5

(2) INFORMATION FOR SEQ ID NO: 104

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104

RTTGTYTCC CGRACGCARG GCACGCACCC RGG

33

(2) INFORMATION FOR SEQ ID NO: 105

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105

CGTGGGRGTS AGCGCYACCC AGCARCGGGA GSW

33

(2) INFORMATION FOR SEQ ID NO: 106

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106

15

YGTRGTGGGG AYGCTGKHRT TCCTGGCCGC VAR

33

(2) INFORMATION FOR SEQ ID NO: 107

(i) SEQUENCE CHARACTERISTICS:

20

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107

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CCCRACGAGC AARTCGACRT GRCGTCGTAW TGT

33

(2) INFORMATION FOR SEQ ID NO: 108

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10

- (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108
YCCCACGTAC ATAGCSGAMS AGARRGYAGC CGY

33

15

(2) INFORMATION FOR SEQ ID NO: 109

- 20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

- (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109
CTGGGAGAYR AGRAAAACAG ATCCGCARAG RTC

33

(2) INFORMATION FOR SEQ ID NO: 110

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110

YGTCTCRTGC CGGCCAGSBG AGAAGGTGAA YAG 33

15 (2) INFORMATION FOR SEQ ID NO: 111

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111

GCCGGGATAG AKKGAGCART TGCAKTCCTG YAC 33

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(2) INFORMATION FOR SEQ ID NO: 112

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112

CATATCCCAA GCCATRCGRT GGCCTGAYAC CTG

33

(2) INFORMATION FOR SEQ ID NO: 113

15

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113

25 CACTARGGCT GYYGTRGGYG ACCAGTTCAT CAT

33

(2) INFORMATION FOR SEQ ID NO: 114

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- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116
SCCCACCATG GAWWAGTAGG CAAGGCCCGC YAG

33

10 (2) INFORMATION FOR SEQ ID NO: 117

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117
GAGTAGCATC ACAATCAADA CCTTAGCCCA GTT

33

(2) INFORMATION FOR SEQ ID NO: 118

- 25 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 nucleotides
 - (B) TYPE: nucleic acid

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----- (C) STRANDEDNESS: single -----

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118

YGWCRYGYRG GTRTKCCCGT CAACGCCGGC AAA

33

(2) INFORMATION FOR SEQ ID NO: 119

10

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119

20

TCCTCACAGG GGAGTGATTC ATGGTGGAGT GTC

33

(2) INFORMATION FOR SEQ ID NO: 120

(i) SEQUENCE CHARACTERISTICS:

25

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120
ATGGCTAGAC GCTTTCTGCG TGAAGACAGT AGT

33

(2) INFORMATION FOR SEQ ID NO: 121

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121
GCCTGGAGGC TGCACGRCAC TCATACTAAC GCC

33

20 (2) INFORMATION FOR SEQ ID NO: 122

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122
CGCAGACCAC TATGGCTCTY CCGGGAGGGG GGG

33

5

(2) INFORMATION FOR SEQ ID NO: 123

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123
TCRTCCYGGC AATTCCGGTG TACTCACCGG TTC

33

15

(2) INFORMATION FOR SEQ ID NO: 124

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

20

25

(ii) MOLECULE TYPE: DNA

- 139 -

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124

GCATIGAGCG GGTTCATCCA AGAAAGGACC CGG

33

(2) INFORMATION FOR SEQ ID NO: 125

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125

15

AGCAGTCTYG CGGGGGCACG CCCAARTCTC CAG

33

(2) INFORMATION FOR SEQ ID NO: 126

(i) SEQUENCE CHARACTERISTICS:

20

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126

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-----ACAAGGCCTT TCGCGACCCA ACACTACTCG GCT-----

33

(2) INFORMATION FOR SEQ ID NO: 127

5

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127

GGGGCACTCG CAAGCACCCCT ATCAGGCAGT ACC

33

15

(2) INFORMATION FOR SEQ ID NO: 128

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

20

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(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128

5 YGTGCTCATG RTGCACGGTC TACGAGACCT CCC 33

(2) INFORMATION FOR SEQ ID NO: 129

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129

GTTACGTTTG KTTYTTYTTT GRGGTTTRGG AWT 33

20 (2) INFORMATION FOR SEQ ID NO: 130

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130

CGGGAACTTR ACGTCCTGTG GCGRCGGTT GGT

33

5

(2) INFORMATION FOR SEQ ID NO: 131

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

10

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131

CARGTAAACT CCACCRACGA TCTGRCCRCC RCC

33

(2) INFORMATION FOR SEQ ID NO: 132

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

25

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132

RCGCACACCC AAYCTRGGGC CCCTGCGCGG CAA

33

5 (2) INFORMATION FOR SEQ ID NO: 133

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133

15 AGGTTGCGAC CGCTCGGAAG TCTTYCTRGT CGC

33

(2) INFORMATION FOR SEQ ID NO: 134

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134

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RCGHRCCTTG GGGATAGGCT GACGTCWACC TCG

33

(2) INFORMATION FOR SEQ ID NO: 135

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10

- (ii) MOLECULE TYPE: DNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135
RCGHRCCTTG GGGATAGGTT GTCGCCWTCC ACG

33

15 (2) INFORMATION FOR SEQ ID NO: 136

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
20 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: DNA

- 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136
YCCRGGCTGR GCCCAGRYCC TRCCCTCGGR YYG

33

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(2) INFORMATION FOR SEQ ID NO: 137

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137

BSHRCCCTCR TTRCCRTAGA GGGGCCADGG RTA 33

(2) INFORMATION FOR SEQ ID NO: 138

15

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138

25 GCCRCGGGGW GACAGGAGCC ATCCYGCCCA CCC 33

(2) INFORMATION FOR SEQ ID NO: 139

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- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
5 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139
CCGGGGGTCY GTGGGGCCCC AYCTAGGCCG RGA 33
- (2) INFORMATION FOR SEQ ID NO: 140
- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 20 (ii) MOLECULE TYPE: DNA
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140
ATCGATGACC TTACCCAART TRCGCGACCT RCG 33
- 25 (2) INFORMATION FOR SEQ ID NO: 141
- (i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141
CCCCATGAGR TCGGCGAAGC CGCAYGTRAG GGT

33

10

(2) INFORMATION FOR SEQ ID NO: 142

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142
GCCYCCWARR GGGGCGCCGA CGAGCGGWAT RTA

33

(2) INFORMATION FOR SEQ ID NO: 143

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 nucleotides
- (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 143

AACCCGGACR CCRTGYGCCA RGGCCCTGGC AGC 33

(2) INFORMATION FOR SEQ ID NO: 144

10 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144

RTTCCCTGTT GCATAGTTCA CGCCGTCYTC CAG 33

20

(2) INFORMATION FOR SEQ ID NO: 145

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 nucleotides

25 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145

5 CARRAGGAAG AKAGAGAAAG AGCAACCRGG MAR 33

(2) INFORMATION FOR SEQ ID NO: 146

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146

AGGCATAGGA CCCGTGTCTT 20

20 (2) INFORMATION FOR SEQ ID NO: 147

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 20 nucleotides
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147

CTTCTTTGGA GAAAGTGGTG 20

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CLAIMS

1. As a composition of matter, a non-naturally occurring nucleic acid having a non-HCV-1 nucleotide sequence of eight or more nucleotides corresponding to a nucleotide sequence within the hepatitis C virus genome.
2. The composition of claim 1 wherein said nucleotide sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome is selected from the regions consisting of the NS5 region, envelope 1 region, 5'UT region, and the core region.
3. The composition of claim 1 wherein said nucleotide sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the NS5 region.
4. The composition of claim 3 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome is selected from a sequence within sequences numbered 2-22.

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5. The composition of claim 1 wherein said nucleotide sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the envelope 1 region.

5

6. The composition of claim 5 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome corresponds to a sequence within sequence numbers 24-32.

10

7. The composition of claim 1 wherein at least one sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the 5'UT region.

15

8. The composition of claim 7 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome corresponds to a sequence within sequences numbered 34-51.

20

9. The composition of claim 1 wherein said nucleotide sequence corresponding to a non-HCV-1 nucleotide sequence within the hepatitis C virus genome corresponds to a sequence in the core region.

10. The composition of claim 9 wherein said nucleotide sequence corresponding to a non-HCV-1 sequence within the hepatitis C virus genome corresponds to a within sequences numbered 53-66.

5

11. The composition of claim 1 wherein said non-naturally occurring nucleic acid has a nucleotide sequence corresponding to one or more genotypes of hepatitis C virus.

10

12. The composition of claim 11 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a first genotype which first genotype is defined substantially by sequences numbered 1-6 in the NS5 region, 23-25 in the envelope 1 region, 33-38 in the 5'UT region, and 52-57 in the core region.

13. The composition of claim 11 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a second genotype which second genotype is defined substantially by sequences numbered 7-12 in the NS5 region, 26-28 in the envelope 1 region, 39-45 in the 5'UT region, and 58-64 in the core region.

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14. The composition of claim 11 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences
5 numbered 13-17 in the NS5 region, 32 in the envelope 1 region, 46-47 in the 5'UT region and 65-66 in the core region.

15. The composition of claim 11 wherein said
10 non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

15
16. The composition of claim 11 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences
20 numbered 18-19 in the NS5 region and 50-51 in the 5'UT region.

17. The composition of claim 1 wherein said non-naturally occurring nucleic acid is capable of
25 priming a reaction for the synthesis of nucleic acid to form a nucleic acid having a nucleotide sequence corresponding to hepatitis C virus.

18. The composition of claim 1 wherein said non-naturally occurring nucleic acid has label means for detecting a hybridization product.
- 5 19. The composition of claim 1 wherein said non-naturally occurring nucleic acid has support means for separating a hybridization product from solution.
- 10 20. The composition of claim 1 wherein said non-naturally occurring nucleic acid prevents the transcription or translation of viral nucleic acid.
- 15 21. A method of forming a hybridization product with a hepatitis C virus nucleic acid comprising the following steps:
- 20 a. placing a non-naturally occurring nucleic acid having a nucleotide sequence of eight or more nucleotides corresponding to a non-HCV-1 sequence in the hepatitis C viral genome into conditions in which hybridization conditions can be imposed said non-naturally occurring nucleic acid capable of forming a
- 25 hybridization product with said hepatitis C virus nucleic acid under hybridization conditions; and

- b. imposing hybridization conditions to form a hybridization product in the presence of hepatitis C virus nucleic acid.

5 22. The method of claim 21 wherein said nucleotide
sequence corresponding to a non-HCV-1 sequence in the
hepatitis C virus genome corresponds to a sequence
within at least one of the regions consisting
essentially of NS5 region, envelope 1 region, 5'UT
10 region, and the core region.

23. The method of claim 21 wherein said nucleotide
sequence corresponds to a non-HCV-1 sequence
corresponds to a sequence within the NS5 region.

15

24. The method of claim 23 wherein said nucleotide
sequence corresponds to a non-HCV-1 sequence
corresponds to a sequence within sequences numbered
2-22.

20

25. The method of claim 21 wherein said nucleotide
sequence corresponds to a non-HCV-1 sequence
corresponds to a sequence within the envelope 1 region.

26. The method of claim 25 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence is selected from a sequence within sequences numbered 24-32.
- 5
27. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence corresponding to a sequence within the 5'UT region.
- 10
28. The method of claim 27 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence selected from a sequence within sequences numbered 34-51.
- 15
29. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence corresponding to a sequence within the core region.
- 20
30. The method of claim 29 wherein said nucleotide sequence corresponds to a non-HCV-1 sequence selected from a sequence within sequences numbered 53-66.
- 25
31. The method of claim 21 wherein said nucleotide sequence corresponds to a non-HCV-1 nucleotide sequence corresponding to one or more genotypes of hepatitis C virus.

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32. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a first genotype which first genotype is defined substantially by sequences numbered 1-6 in the NS5 region, 23-25 in the envelope 1 region, 33-38 in the 5'UT region, and 52-57 in the core region.

33. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a second genotype which second genotype is defined substantially by sequences numbered 7-12 in the NS5 region, 26-28 in the envelope 1 region, 39-45 in the 5'UT region, and 58-64 in the core region.

34. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences numbered 13-17 in the NS5 region, 32 in the envelope 1 region, 46-47 in the 5'UT region and 65-66 in the core region.

35. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

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36. The method of claim 21 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences numbered 18-19 in the NS5 region and 50-51 in the 5'UT region.

37. The method of claim 21 wherein said hybridization product is capable of priming a reaction for the synthesis of nucleic acid.

38. The method of claim 21 wherein said non-naturally occurring nucleic acid has label means for detecting a hybridization product.

39. The method of claim 21 wherein said non-naturally occurring nucleic acid has support means for separating the hybridization product from solution.

40. The method of claim 21 wherein said non-naturally occurring nucleic acid prevents the transcription or translation of viral nucleic acid.

41. As a composition of matter, a non-naturally occurring polypeptide corresponding to a non-HCV-1 nucleotide sequence of nine or more nucleotides which sequence of nine or more nucleotides corresponds to a sequence within hepatitis C virus genomic sequences.

42. The composition of claim 41 wherein said non-HCV-1 sequence is selected from one of the regions consisting of NS5 region, envelope 1 region, and the core region.
- 5 43. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence corresponds to a sequence in the NS5 region.
- 10 44. The composition of claim 43 wherein said non-HCV-1 sequence is selected from a sequence within sequences numbered 2-22.
- 15 45. The composition of claim 41 wherein said non-HCV-1 sequence corresponds to a sequence in the envelope 1 region.
- 20 46. The composition of claim 45 wherein said non-HCV-1 sequence is selected from a sequence within sequences numbered 24-32.
- 25 47. The composition of claim 41 wherein said non-HCV-1 sequence corresponds to a sequence in the core region.
48. The composition of claim 47 wherein said non-HCV-1 sequence is selected from a sequence within sequences numbered 52-66.

49. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a nucleotide sequence corresponding to one or more genotypes of hepatitis C virus.

5

50. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a first genotype which first genotype is defined substantially by sequences numbered 1-6 in the
10 NS5 region, 23-25 in the envelope 1 region, and 52-57 in the core region.

51. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a
15 sequence of a second genotype which second genotype is defined substantially by sequences numbered 7-12 in the NS5 region, 26-28 in the envelope 1 region, and 58-64 in the core region.

20 52. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences numbered 13-17 in the NS5 region, 32 in the envelope 1 region, and 65-66
25 in the core region.

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53. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

54. The composition of claim 41 wherein said non-HCV-1 nucleotide sequence has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences numbered 18-19 in the NS5 region and 50-51 in the 5'UT region.

55. The composition of claim 41 wherein said polypeptide is capable of generating an immune reaction in a host.

56. An antibody capable of selectively binding to the composition of claim 41.

20

57. A method of detecting one or more genotypes of hepatitis C virus comprising the following steps:

a) placing a non-naturally occurring nucleic acid having a nucleotide sequence of eight or more nucleotides corresponding to one or more genotypes of hepatitis C virus under conditions where hybridization conditions can be imposed,

25

- b) ~~imposing hybridization conditions to form a~~
hybridization product in the presence of hepatitis
C virus nucleic acid; and
c) monitoring the non-naturally occurring nucleic
5 acid for the formation of a hybridization product,
which hybridization product is indicative of the
presence of the genotype of hepatitis C virus.

58. The method of claim 57 wherein said non-naturally
10 occurring nucleic acid has a sequence corresponding to
a sequence of a first genotype which first genotype is
defined substantially by sequences numbered 1-6 in the
NS5 region, 23-25 in the envelope 1 region, 33-38 in
the 5'UT region, and 52-57 in the core region.

15 59. The method of claim 57 wherein said non-naturally
occurring nucleic acid has a sequence corresponding to
a sequence of a second genotype which second genotype
is defined substantially by sequences numbered 7-12 in
20 the NS5 region, 26-28 in the envelope 1 region, 39-45
in the 5'UT region, and 58-64 in the core region.

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60. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a third genotype which third genotype is defined substantially by sequences numbered 13-17 in the NS5 region, 32 in the envelope 1 region, 46-47 in the 5'UT region and 65-66 in the core region.

61. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fourth genotype which fourth genotype is defined substantially by sequences numbered 20-22 in the NS5 region, 29-31 in the envelope 1 region and 48-49 in the 5'UT region.

62. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence of a fifth genotype which fifth genotype is defined substantially by sequences numbered 18-19 in the NS5 region.

63. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 67-145.

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64. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 69, 71, 73 and 81-99 to identify Group I genotypes in the core and region of the HCV genome.

65. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 70, 72, 70 and 100-118 to identify Group II genotypes in the core and envelope regions of the HCV genome.

66. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence corresponding to a sequence numbered 77 to identify Group III genotypes in the 5' UT region of the HCV genome.

67. The method of claim 57 wherein said non-naturally occurring nucleic acid has a sequence numbered 79 to identify Group IV genotypes in the 5' UT region of the HCV genome.

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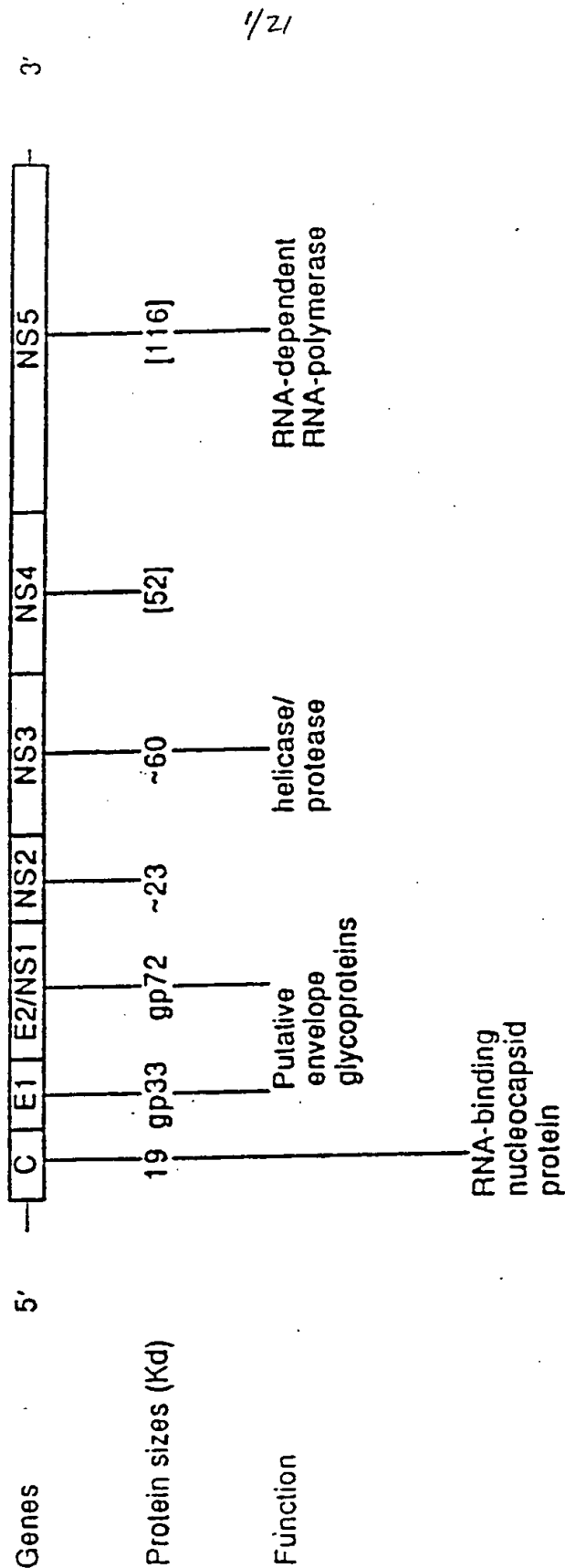


Fig. 1

Fig. 2a

NS5 REGION

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
1	1	GI	CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGACCT CGACCCCCAA
2	1		CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA ATTTACCAAT GTTGTGACCT GGACCCCCAA
3	1		CTCCACAGTC ACTGAGAGCG ACATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGATCT GGACCCCCAA
4	1		CTCTACAGTC ACTGAGAACG ACATCCGTAC GGAGGAGGCA ATTTACCAAT GTTGTGACCT GGACCCCCAA
5	1		CTCCACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGACCT GGACCCCCAA
6	1		CTCTACAGTC ACTGAGAGCG ATATCCGTAC GGAGGAGGCA ATCTACCAAT GTTGTGACCT GGACCCCGAA
7	1	GII	CTCCACAGTC ACTGAGAATG ACACCCGTGT TGAGGAGTCA ATTTACCAAT GTTGTGACTT GGCCCCCGAA
8	1		CTCAACGGTC ACTGAGAATG ACATCCGTGT TGAGGAGTCA ATTTACCAAA GTTGTGACTT GGCCCCCGAG
9	1		CTCAACGGTC ACCGAGAATG ACATCCGTGT TGAGGAGTCA ATTTATCAAT GTTGTGCTT GGCCCCCGAG
10	1		CTCAACGGTC ACTGAGAGTG ACATCCGTGT CGAGGAGTCG ATTTACCAAT GTTGTGACTT GGCCCCCGAA
11	1		CTCCACAGTC ACTGAGAGTG ACATCCGTGT TGAGGAGTCA ATTTACCAAT GTTGTGACTT GGCCCCCGAA
12	1		CTCAACAGTC ACTGAGAGTG ACATCCGTGT TGAGGAGTCA ATCTACCAAT GTTGTGACTT GGCCCCCGAA
13	1	GIII	CTCAACCGTC ACTGAGAGG ACATCAGAAC TGAGGAGTCC ATATACCGAG CTTGCTCCT GCCTGAGGAG
14	1		CTCTACAGTC ACGTAAAGG ACATCACATC CTAGGAGTCC ATCTACCAAT CTTGTTCACT GCCCGAGGAG
15	1		CTCTACAGTC ACAGAGAGGG ACATCAGAAC CGAGGAGTCC ATCTATCTGT CTTGCTCACT GCCTGAGGAG
16	1		CTCTACAGTC ACGGAGAGGG ACATCAGAAC CGAGGAGTCC ATCTATCTGT CTTGTTCACT GCCTGAGGAG
17	1		CTCAACCGTC ACGGAGAGGG ACATAAGAAC AGAAGAATCC ATATATCAGG GTTGTTCCT GCCTCAGGAG
18	1	GV	CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCT ATTTACCAAT CATGTACTT GCAGCCTGAG
19	1		CTCGACCGTT ACCGAACATG ACATAATGAC TGAAGAGTCC ATTTACCAAT CATGTACTT GCAGCCTGAG
20	1	GIV	CTCTACTGTC ACTGAACAGG ACATCAGGT GGAAGAGGAG ATATACCAAT GCTGTAACCT TGAACCGGAG
21	1		CTCGACTGTC ACTGAACAGG ACATCAGGT GGAAGAGGAG ATATACCAAT GCTGTAACCT TGAACCGGAG
22	1		CTCAACTGTC ACTGAACAGG ACATCAGGT GGAAGAGGAG ATATACCAAT GCTGTAACCT TGAACCGGAG

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Fig. 2b

NS5 REGION - (2/5)

SEQUENCE			ID NUMBER		GENOTYPE		SEQUENCE	
=====			=====		+++++		=====	
1	71	GI	GCCCGCGTGG	CCATCAAGTC	CCTCACCGAG	AGGCTTTATG	TTGGGGGCCC	TCTTACCAAT TCAAGGGGGG
2	71	GI	GCCCGCATGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTATG	TCGGGGGCCC	TCTTACCAAT TCAAGGGGGG
3	71	GI	GCCCGCGTGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTACG	TTGGGGGCCC	TCTTACCAAT TCAAGGGGGG
4	71	GI	GCCCGCGTGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTATG	TTGGGGGCCC	TCTTACCAAT TCAAGGGGGG
5	71	GI	GCCCGCGTGG	CCATCAAGTC	CCTCACCGAG	AGGCTTTATG	TCGGGGGCCC	TCTTACCAAT TCAAGGGGGG
6	71	GI	GCCCGTGTGG	CCATCAAGTC	CCTCACTGAG	AGGCTTTATG	TTGGGGGCCC	TCTTACCAAT TCAAGGGGGG
=====			=====		=====		=====	
7	71	GII	GCCAGACAGG	CCATAAGGTC	GCTCACAGAG	CGGCTCTATG	TCGGGGGTCC	TATGACTAAC TCCAAAGGGC
8	71		GCCAGACAAG	CCATAAGGTC	GCTCACAGAG	CGGCTTTACA	TCGGGGGCCC	CCTGACTAAT TCAAAAGGGC
9	71		GCTAGACAGG	CCATAAGGTC	GCTCACAGAG	CGGCTTTATA	TCGGGGGCCC	CCTGACCAAT TCAAAAGGGC
10	71		GCCAGGCAGG	CCATAAGGTC	GCTCACCGAG	CGACTTTATA	TCGGGGGCCC	CCTGACTAAT TCAAAAGGGC
11	71		GCCAGACAGG	CTATAAGGTC	GCTCACAGAG	CGGCTGTACA	TCGGGGGTCC	CCTGACTAAT TCAAAAGGGC
12	71		GCCAGACAGG	CTATAAGGTC	GCTCACAGAG	CGGCTTTACA	TCGGGGGTCC	CCTGACTAAT TCAAAAGGGC
=====			=====		=====		=====	
13	71	GIII	GCTCACATTG	CCATACACTC	GCTGACTGAG	AGGCTCTACG	TGGGAGGGCC	CATGTTCAAC AGCAAGGGCC
14	71		GCTCGAATG	CTATACACTC	ACTGACTGAG	AGACTATACG	TAGGGGGGCC	CATGACAAAC AGCAAGGGCC
15	71		GCCCGAATG	CTATACACTC	ACTGACTGAG	AGACTGTACG	TAGGGGGGCC	CATGACAAAC AGCAAGGGCC
16	71		GCTCGAATG	CCATACACTC	ACTGACTGAG	AGGCTGTACG	TAGGGGGGCC	CATGACAAAC AGCAAGGGCC
17	71		GCTAGAATG	CTATCCACTC	GCTCACTGAG	AGACTCTACG	TAGGAGGGCC	CATGACAAAC AGCAAGGGAC
=====			=====		=====		=====	
18	71	GV	GCGGTGTGG	CAATACGGTC	ACTCACCCAA	CGCCTGTACT	GTGGAGGGCC	CATGTATAAC AGCAAGGGCC
19	71		GCACGCGCG	CAATACGGTC	ACTCACCCAA	CGCCTGTACT	GTGGAGGGCC	CATGTATAAC AGCAAGGGCC
=====			=====		=====		=====	
20	71	GIV	GCCAGGAAG	TGATCTCTC	CCTCAGGAG	CGGCTTTACT	GCGGGGGCCC	TATGTTCAAC AGCAAGGGGG
21	71		GCCAGGAAG	TGATCTCTC	CCTCAGGAG	CGGCTTTACT	GCGGGGGCCC	TATGTTCAAT AGCAAGGGGG
22	71		GCCAGGAAG	TGATCTCTC	CCTCAGGAA	CGGCTTTACT	GCGGGGGCCC	TATGTTCAAC AGCAAGGGGG
=====			=====		=====		=====	

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Fig. 2c

NS5 REGION - (3/5)

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
1	141	GI	AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
2	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
3	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
4	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
5	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
6	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
7	141	GI	AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
8	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
9	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
10	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
11	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
12	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
13	141	GI	AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
14	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
15	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
16	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
17	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
18	141	GV	AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
19	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
20	141	GI	AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
21	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG
22	141		AGAACTGCGG CTATCGCAGG TGCCGCGCGA GCGGCGTACT GACAACTAGC TGTTGGTAACA CCCTCACCTG

Fig. 2d

NS5 REGION - (4/5)

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SEQUENCE	ID NUMBER	GENOTYPE	
1	211	GI	CTACATCAAG GCCCGGGCAG CCTGTCGAGC CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC
2	211		CTACATCAAG GCCCGGGCAG CCTGTCGAGC CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC
3	211		CTACATCAAG GCCCGGGCAG CCTGTCGAGC CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC
4	211		CTACATTAAG GCCCGGGCAG CCTGTCGAGC CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC
5	211		TTACATCAAG GCCCAAGCAG CCTGTCGAGC CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC
6	211		TTACATCAAG GCCCGGGCAG CCTGTCGAGC CGCAGGGCTC CAGGACTGCA CCATGCTCGT GTGTGGCGAC
7	211	GII	CTACCTGAAG GCCACAGCGG CCTGTCGAGC TGCCAAGCTC CAGGACTGCA CGATGCTCGT GAACGGAGAC
8	211		TTACTTGAAG GCCACTGCGG CCTGTAGAGC TGCGAAGCTC CAGGACTGCA CGATGCTCGT GTGCGGAGAC
9	211		TTACTTGAAG GCCTCTGCAG CCTGTCGAGC CGCAGGAGCTC CAGGACTGCA CGATGCTCGT GTGTGGGGAC
10	211		TTACTTGAAG GCCTCTGCAG CCTGTCGAGC TGCAAAAGCTC CAGGACTGCA CGATGCTCGT GAACGGGGAC
11	211		TTACTTGAAG GCCTCTGCAG CCTGTCGAGC TGCGAAGCTC CAGGACTGCA CGATGCTCGT GTGCGGTGAC
12	211		TTACCTGAAG GCCAGTGCGG CCTGTCGAGC TGCGAAGCTC CAGGACTGCA CAATGCTCGT GTGCGGTGAC
13	211	GIII	CTATGTAAA GCCCTAGCGG CTTGCAAGGC TGCAGGGATA GTTGACCCCT CAATGCTCGT ATGCGGGCAG
14	211		CTACGTAAA GCCAGGGCGG CGTGTAAACG CGCGGGGATT GTTGCTCCCA CCATGCTCGT GTGCGGTGAC
15	211		CTACGTAAA GCCAGAGCGG CGTGTAAACG CGCGGGCATT GTTGCTCCCA CCATGTTGCT GTGCGGGCAG
16	211		CTACGTAAA GCTAAAGCGG CATGTAAACG CGCGGGCATT GTTGCCCCCA CCATGTTGCT GTGCGGGCAG
17	211		CTACATCAA GCCCTTGACG CGTGCAAGC TGCAGGGATC GTGGACCTA TCATGCTGCT GTGTGGAGAC
18	211	GV	CTACATTAAG GCCTTAGCCT CCTGTAGAGC CGCAAGCTC CAGGACTGCA CGCTCCTGCT GTGTGGTGTG
19	211		CTACATCAAG GCCTCAGCCG CCTGTAGAGC TGCAAAGCTC CAGGACTGCA CGCTCCTGCT GTGTGGTGTG
20	211	GIV	TTACATCAAG GCTAGAGCGG CTTCGAAGC CGCAGGCCTC CGGAACCCGG ACTTCTTGT CTGCGGAGAT
21	211		TTACATCAAG GCTAGAGCGG CTTCGAAGC CGCAGGCCTC CGGAACCCGG ACTTCTTGT CTGCGGAGAT
22	211		TTACATCAA GCTAGAGCGG CTGCGGAAGC CGCAGGCCTC CGGAACCCGG ACTTCTTGT CTGCGGAGAT

Fig. 2e

NS5 REGION - (5/5)

SEQUENCE	ID NUMBER	GENOTYPE	
1	281	GI	GACTTAGTCG TTATCTGTGA AAGCGCGGG GTCCAGGAG ACGCGGCGAG CCTGAGAGCC
2	281		GACTTAGTCG TTATCTGTGA AAGTCGCGG GTCCAGGAG ACGCGGCGAG CCTGAGAGCC
3	281		GACTTGGTCG TTATCTGTGA GAGTCGCGG GTCCAGGAG ACGCGGCGAG CCTGAGAGCC
4	281		GACTTAGTCG TTATCTGTGA GAGTCGCGG GTCCAGGAG ACGCGGCGAA CCTGAGAGCC
5	281		GACTTAGTCG TTATCTGTGA AAGTCAGGGA GTCCAGGAG ATGCAGCGAA CCTGAGAGCC
6	281		GACCTAGTCG TTATCTGCGA AAGTCGCGG GTCCAGGAG ACGCGGCGAG CCTGAGAGCC
7	281	GII	GACCTTGTG TTATCTGTGA AAGCGCGGG AACCAAGAG ACGCGGCAAG CCTACGAGCC
8	281		GACCTTGTG TTATCTGTGA AAGCGCGGGA ACCCAGGAG ATGCGGCGAG CCTACGAGTC
9	281		GACCTTGTG TTATCTGTGA AAGCGCGGGA ACCCAGGAG ACGCGGCGAA CCTACGAGTC
10	281		GACCTTGTG TTATCTGCGA GAGCGCGGGA ACCCAAGAG ACGCGGCGAG CCTACGAGTC
11	281		GACCTTGTG TTATCTGTGA GAGCGCGGGA ACCCAAGAG ACGCGGCGAG CCTACGAGTC
12	281		GACCTTGTG TTATCTGTGA GAGCGCGGG ACCCAAGAG ACGCGGCGAG CCTACGAGTC
13	281	GIF	GACTTAGTTG TCATCTCAGA AAGCCAGGG ACTGAGGAG ACGAGCGGAA CCTGAGAGCT
14	281		GACCTGGTCG TCATCTCAGA GAGTCAAGG GCTGAGGAG ACGAGCAGAA CCTGAGAGTC
15	281		GACCTGGTTG TCATCTCAGA GAGTCAAGG GTCGAGGAG ATGAGCGGAA CCTGAGAGTC
16	281		GACCTAGTCG TCATCTCAGA GAGTCAAGG GTCGAGGAG ATGAGCGGAA CCTGAGAGCT
17	281		GACCTGGTCG TCATCTCGA GAGCGAAGT AACGAGGAG ACGAGCGGAA CCTGAGAGCT
18	281	GV	GATCTTGTG CCATTTCGA GAGCCAGGG ACGCACGAG ATAAAGCGAG CCTGAGAGCC
19	281		ACCTTGGTGG CCATTTCGA GAGCCAAAG ACGCACGAG ATGAAGCGTG CCTGAGAGTC
20	281	GIV	GATCTGGTCG TGGTGGCTGA GAGTGATGG GTCGACGAG ATAGAGCAGC CCTGAGAGCC
21	281		GATCTGGTTG TGGTGGCTGA GAGTGATGG GTCGACGAG ATAGAACAGC CCTGCGAGCC
22	281		GATCTGGTTG TGGTGGCTGA GAGTGATGG GTCATGAGG ATAGAGCAGC CCTGGGAGCC

340 TOTAL

Fig. 3

ENVELOPE REGION

SEQUENCE ID NUMBER	GENOTYPE	
23	GI 1	GACGGCGTTG GTAATGGCTC AGCTGCTCCG GATCCACAA GCCATCTGG ACATGATCGC
24	1	GACGGCGTTG GTGGTAGCTC AGGTACTCCG GATCCACAA GCCATCATGG ACATGATCGC
25	1	AACGGCGCTG GTAGTAGCTC AGCTGCTCAG GGTCCCGCAA GCCATCGTGG ACATGATCGC
26	GII 1	GACAGCCCTA GTGGTATCGC AGTTACTCCG GATCCACAA GCCGTCATGG ATATGGTGGC
27	1	AGCAGCCCTA GTGGTATCGC AGTTACTCCG GATCCACAA AGCATCGTGG ACATGGTGGC
28	1	GGCAGCCCTA GTGGTATCGC AGTTACTCCG GATCCCGCAA GCTGTGCTGG ACATGGTGGC
29	GIV 1	TGTGGGTATG GTGGTGGCGC AGTCTCTGGC TTGGCCCGAG ACCTTGTTTCG ACATAATAGC
30	1	TGTGGGTATG GTGGTAGCAC AGTCTCTGGC TCTGGCCCGAG ACCTTGTTTCG ACATAATAGC
31	1	TGTGGGTATG GTGGTGGCGC AAGTCTCTGG TTGGCCCGAG ACCTTGTTTCG ACGTGCTAGC
32	GIII 1	TACCACTATG CTCCTGGCAT ACTTGGTGCG CATCCCGGAG GTCATCCTGG ACATTATCAC
23	GI 61	TGCTGCTCAC TGGGGAGTCC TGGCGGGCAT AGCGTATTTT
24	61	TGGAGCCAC TGGGGAGTCC TGGCGGGCAT AGCGTATTTT
25	61	TGCTGCTCAC TGGGGAGTCC TAGCGGGCAT AGCGTATTTT
26	GII 61	GGGGCCAC TGGGGAGTCC TGGCGGGCCT TGCCTACTAT
27	61	GGGGCCAC TGGGGAGTCC TGGCGGGCCT TGCCTACTAT
28	61	GGGGCCAC TGGGGAATCC TAGCGGGTCT TGCCTACTAT
29	GIV 61	CGGGCCCAT TGGGGCATCT TGGCGGGCCT GGCCTATTAC
30	61	CGGGCCCAT TGGGGCATCT TGGCAGGCCT AGCCTATTAC
31	61	CGGGCCCAT TGGGGCATCT TGGCGGGCCT GGCCTATTAC
32	GIII 61	GGGAGGACAC TGGGGCGTGA TGTTTGGCCT GGCTTATTTT

SUBSTITUTE SHEET

Fig. 4a

5'UT Region

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
33	GI	1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
34		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
35		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
36		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
37		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
38		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
39	GII	1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
40		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
41		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
42		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
43		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
44		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
45		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
46	GIII	1	GCTAGTATCA GTGTCGTGCA GCCTCCAGGC CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
47		1	GTTAGTATGA GTGTCGTGCA GCCTCCAGGC CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
48	GIV	1	GTTAGTACGA GTGTCGTGCA GCCTCCAGGA CTCCTCCCTCC CGGGAGAGCC ATAGTGGTCT
49		1	GTTAGTACGA GTGTCGTGCA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
50	GV	1	GTTAGTATGA GTGTCGAACA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT
51		1	GTTAGTATGA GTGTCGAACA GCCTCCAGGA CCCCCCCTCC CGGGAGAGCC ATAGTGGTCT

Fig. 4b

5'UT Region (2/5)

9/21

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
33	61	GI	GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
34	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
35	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
36	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
37	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
38	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
39	61	GII	GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
40	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
41	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
42	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
43	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
44	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
45	61		GC GGAACCGG TGAGTACACC GGAATTGCCA GGACGACCGG GTCCTTTCTT GGATCAACCC
46	61	GIII	GC GGAACCGG TGAGTACACC GGAATTGCCG GGAAGACTGG GTCCTTTCTT GGATCAACCC
47	61		GC GGAACCGG TGAGTACACC GGAATTGCCG GGAAGACTGG GTCCTTTCTT GGATCAACCC
48	61	GIV	GC GGAACCGG TGAGTACACC GGAATCGCTG GGGTGACCGG GTCCTTTCTT GGAGCAACCC
49	61		GC GGAACCGG TGAGTACACC GGAATCGCTG GGGTGACCGG GTCCTTTCTT GGAGTAACCC
50	61	GV	GC GGAACCGG TGAGTACACC GGAATTGCCG GGATGACCGG GTCCTTTCTT GGATCAACCC
51	61		GC GGAACCGG TGAGTACACC GGAATTGCCG GGATGACCGG GTCCTTTCTT GGATCAACCC

10/21

Fig. 4c

5'UT Region (3/5)

SEQUENCE			ID NUMBER		GENOTYPE		
33	121	GI	121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
34	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
35	121		121	121	GCTCAATGCC	TGGAGATTG	GGCACGCCCC CGCAAGATCA CTAGCCGAGT AGTGTGGGT
36	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
37	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
38	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGTGTGGGT
39	121	GII	121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
40	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
41	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
42	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
43	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
44	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
45	121		121	121	GCTCAATGCC	TGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
46	121	GIII	121	121	ACTCTATGCC	CGGCCATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGCGTTGGT
47	121		121	121	ACTCTATGCC	CAGCCATTG	GGCGTGCCCC CGCAAGACTG CTAGCCGAGT AGCGTTGGT
48	121	GIV	121	121	GCTCAATACC	CAGAAATTG	GGCGTGCCCC CGCGAGATCA CTAGCCGAGT AGTGTGGGT
49	121		121	121	GCTCAATACC	CAGAAATTG	GGCGTGCCCC CGCGAGATCA CTAGCCGAGT AGTGTGGGT
50	121	GV	121	121	GCTCAATGCC	CGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT
51	121		121	121	GCTCAATGCC	CGGAGATTG	GGCGTGCCCC CGCGAGACTG CTAGCCGAGT AGTGTGGGT

Fig. 4d

ENVELOPE REGION (4/5)

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
33	181	GI	CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
34	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
35	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
36	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
37	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
38	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
39	181	GII	CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
40	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
41	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
42	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
43	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
44	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
45	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
46	181	GIII	TGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
47	181		TGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
48	181	GIV	CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT
49	181		CGCGAAAGGC CTTGTGGTAC TGCTGATAG GGTGCTTGG AGTGCCCCGG GAGGTCTCGT

Fig. 4e

5'UT Region (5/5)

SEQUENCE	ID NUMBER	GENOTYPE
33	GI	241 AGACCGTGCA CC
34		241 AGACCGTGCA CC
35		241 AGACCGTGCA CC
36		241 AGACCGTGCA CC
37		241 AGACCGTGCA CC
38		241 AGACCGTGCA CC
39	GII	241 AGACCGTGCA CC
40		241 AGACCGTGCA TC
41		241 AGACCGTGCA CC
42		241 AGACCGTGCA CC
43		241 AGACCGTGCA CC
44		241 AGACCGTGCA CC
45		241 AGACCGTGCA CC
46	GIII	241 AGACCGTGCA TC
47		241 AGACCGTGCA TC
48	GIV	241 AGACCGTGCA AC
49		241 AGACCGTGCA AC
252 Total		

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Fig. 5a

CORE REGION

SEQUENCE ID NUMBER	GENOTYPE	
52	GI	ATGAGCACGA ATCCTAAACC TCAAGAGAAA AACAAACGTA ACACCAACCG TCGCCCCACAG
53		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG
54		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG
55		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG
56		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG
57		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG
58	GII	ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG
59		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG
60		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG TCGCCCCACAG
61		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG
62		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG
63		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG
64		ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAACGTA ACACCAACCG CCGCCCCACAG
65	GIII	ATGAGCACGA ATCCTAAACC TCAAGAGAAA ACCAAAGAAA ACACCTAACCG CCGCCCCACAG
66		ATGAGCACGA ATCCTCAACC TCAAGAGAAA ACCAAAGAAA ACACCTAACCG CCGCCCCACAG

Fig. 5b

CORE REGION (2/9)

SEQUENCE	ID NUMBER	GENOTYPE	
52	61	GI	GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
53	61		GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
54	61		GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
55	61		GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
56	61		GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
57	61		GACGTCAAGT TCCCGGGTGG CCGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
58	61	GII	GACGTCAAGT TCCCGGGCGG TGGCCAGGTC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG
59	61		GACGTCAAGT TCCCGGGCGG TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG
60	61		GACGTCAAGT TCCCGGGCGG TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG
61	61		GACGTCAAGT TCCCGGGCGG TGGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
62	61		GACGTCAAGT TCCCGGGCGG TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG
63	61		GACGTCAAGT TCCCGGGCGG TGGTCAGATC GTTGGTGGAG TTTACTTGTG GCCGCGCAGG
64	61		GACGTCAAGT TCCCGGGCGG TGGTCAGATC GTTGGTGGAG TTTACCTGTT GCCGCGCAGG
65	61	GIII	GACGTCAAGT TCCCGGGCGG TGGCCAGATC TATACCTGCT GCCGCGCAGG
66	61		GACGTCAAGT TCCCGGGCGG TGGTCAGATC TATACCTGCT GCCGCGCAGG

LITERATUR

15721

Fig. 5c

CORE REGION (3/9)

SEQUENCE	ID NUMBER	GENOTYPE	
52	GI	121	GGCCCTAGAT TGGGTGTCG CGCGACGAGA AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
53		121	GGCCCTAGAT TGGGTGTCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
54		121	GGCCCTAGAT TGGGTGTCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
55		121	GGCCCTAGAT TGGGTGTCG CACGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
56		121	GGCCCTAGAT TGGGTGTCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGAGGT
57		121	GGCCCTAGAT TGGGTGTCG CGCGACGAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGT
58	GII	121	GGCCCCAGGT TGGGTGTCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
59		121	GGCCCCAGGT TGGGTGTCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
60		121	GGCCCCAGGT TGGGTGTCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
61		121	GGCCCCAGGT TGGGTGTCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
62		121	GGCCCCAGGT TGGGTGTCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
63		121	GGCCCCAGGT TGGGTGTCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
64		121	GGCCCCAGGT TGGGTGTCG CGCGACTAGG AAGACTTCCG AGCGGTGCGA ACCTCGTGGG
65	GIII	121	GGCCCCAGAT TGGGTGTCG CGCGACGAGG AAAACTTCCG AACGATCCCA GCCACGCGGA
66		121	GGCCCCAGGT TGGGTGTCG CGCGACGAGG AAAACTTCCG AACGATCCCA GCCACGTTGG

Fig. 5d

CORE REGION (4/9)

SEQUENCE	ID NUMBER	GENOTYPE	
52	181	GI	AGACGTCAGC CTATCCCCAA GGCTCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG
53	181		AGACGTCAGC CTATCCCCAA GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG
54	181		AGACGTCAGC CTATCCCCAA GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG
55	181		AGACGTCAGC CCATCCCCAA GGCTCGTCGA CCCGAGGGCA GGACCTGGGC TCAGCCCGGG
56	181		AGACGTCAGC CTATCCCCAA GGCGCGTCGG CCCGAGGGTA GGACCTGGGC TCAGCCCGGG
57	181		AGACGCCAGC CTATCCCCAA GGCGCGTCGG CCCGAGGGCA GGACCTGGGC TCAGCCCGGG
58	181	GI	AGCGGACAAC CTATCCCCAA GGCTCGCCAG CCCGAGGGCA GGCGCTGGGC TCAGCCCGGG
59	181		AGCGGACAAC CTATCCCCAA GGCTCGCCAG CCCGAGGGCA GGCGCTGGGC TCAGCCCGGG
60	181		AGCGGACAAC CTATCCCCAA GGCTCGCCAG CCCGAGGGCA GGCTCTGGGC TCAGCCCGGG
61	181		AGCGGACAAC CTATCCCCAA GGCTCGCCAG CCCGAGGGTA GGCGCTGGGC TCAGCCCGGG
62	181		AGCGGACAAC CTATCCCCAA GGCTCGCCAG CCCGAGGGCA GGCGCTGGGC TCAGCCCGGG
63	181		AGCGGACAAC CTATCCCCAA GGCTCGCCAG CCCGAGGGCA GGCGCTGGGC TCAGCCCGGG
64	181		AGCGGACAAC CTATCCCCAA GGCTCGCCAG CCCGAGGGCA GGCGCTGGGC TCAGCCCGGG
65	181	GII	AGCGGTCAGC CCATCCCTAA AGATCGTCGC ACCGCTGGCA AGTCCTGGGG AGGCCAGGA
66	181		AGCGGCCAGC CCATCCCTAA AGATCGGGC ACCACTGGCA AGTCCTGGGG GAAGCCAGGA

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Fig. 5e

CORE REGION (5/9)

SEQUENCE	ID NUMBER	GENOTYPE	
52	241	GI	TACCCCTTGGC CCCTCTATGG CAATGAGGGC TGCGGGGTGGG CCGGATGGCT CCTGTCTCCC
53	241		TACCCCTTGGC CCCTCTATGG CAATGAGGGT TGCGGGGTGGG CCGGATGGCT CCTGTCTCCC
54	241		TACCCCTTGGC CCCTCTATGG TAATGAGGGT TGCGGATGGG CCGGATGGCT CCTGTCTCCC
55	241		TACCCCTTGGC CCCTCTATGG CAATGAGGGC TGCGGGGTGGG CCGGATGGCT CCTGTCTCCC
56	241		TACCCCTTGGC CCCTCTATGG CAATGAGGGT TGCGGGGTGGG CCGGATGGCT CCTGTCTCCC
57	241		TACCCCTTGGC CCCTCTATGG CAATGAGGGT TGCGGGGTGGG CCGGATGGCT CCTGTCTCCC
58	241	GII	TACCCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG CAGGATGGCT CCTGTCACCC
59	241		TACCCCTTGGC CCCTCTATGG CAACGAGGGT ATGGGGTGGG CAGGATGGCT CCTGTCACCC
60	241		TACCCCTTGGC CCCTCTATGG CAACGAGGGT ATGGGGTGGG CAGGATGGCT CCTGTCACCC
61	241		TACCCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG CAGGATGGCT CCTGTCTCCC
62	241		TATCCCTTGGC CCCTCTATGG CAATGAGGGT CTGGGGTGGG CAGGATGGCT CCTGTCACCC
63	241		TACCCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG CAGGATGGCT CCTGTCACCC
64	241		TACCCCTTGGC CCCTCTATGG CAATGAGGGT ATGGGGTGGG CAGGATGGCT CCTGTCACCC
65	241	GI	TATCCCTTGGC CCCTGTATGG GAATGAGGGT CTCGGCTGGG CAGGATGGCT CCTGTCTCCC
66	241		TACCCCTTGGC CCCTGTATGG GAATGAGGGT CTCGGCTGGG CAGGATGGCT CCTGTCTCCC

Fig. 5f

CORE REGION (6/9)

SEQUENCE	ID NUMBER	GENOTYPE	
52	301	GI	CGTGGCTCTC GGCCTAGCTG GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT
53	301		CGTGGCTCTC GGCCTAGTTG GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT
54	301		CGTGGCTCTC GGCCTAGTTG GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT
55	301		CGTGGCTCTC GGCCTAGCTG GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT
56	301		CGCGGCTCTC GGCCTAAGTG GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT
57	301		CGTGGCTCTC GGCCTAGCTG GGGCCCCACA GACCCCCGGC GTAGGTCGCG CAATTGGGT
58	301	GII	CGTGGCTCTC GGCCTAGTTG GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTGGGT
59	301		CGTGGCTCTC GGCCTAGTTG GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTGGGT
60	301		CGCGGCTCCC GGCCTAGTTG GGGCCCCACG GACCCCCGGC GTAGGTCGCG TAATTGGGT
61	301		CGCGGCTCCC GGCCTAGTTG GGGCCCCACA GACCCCCGGC GTAGGTCGCG TAATTGGGT
62	301		CGCGGCTCTC GGCCTAGCTG GGGCCCCACG GACCCCCGGC GTAGGTCGCG CAACTGGGT
63	301		CGTGGTCTC GGCCTAGTTG GGGCCCCACG GACCCCCGGC GTAGGTCGCG CAATTGGGT
64	301		CGCGGCTCCC GGCCTAGTTG GGGCCCCAAA GACCCCCGGC GTAGGTCGCG TAATTGGGT
65	301	GIII	CGTGGCTCTC GCCCTTCATG GGGCCCCACT GACCCCCGGC ATAGATCAG CAACTGGGT
66	301		CGCGGTTCTC GCCCTTCATG GGGCCCCACT GACCCCCGGC ATAGATCAG CAACTGGGT

Fig. 5h

CORE REGION (8/9)

SEQUENCE	ID NUMBER	GENOTYPE	SEQUENCE
52	421	GI	GGCGCCCTC TTGGAGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
53	421		GGCGCCCTC TTGGAGGCGC TGCCAGGGCT CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
54	421		GGCGCCCTC TTGGAGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
55	421		GGCGCCCTC TTGGAGGCGC TGCCAGAGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
56	421		GGCGCCCTC TTGGAGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
57	421		GGCGCCCTC TTGGAGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
58	421	GII	GGCGCCCTC TTAGGGGCGC TGCCAGGGCC TTGGCGCATG GCGTCCGGGT TCTGGAAGAC
59	421		GGCGCCCTC TAGGGGCGC TGCCAGGGCC CTGGCACATG GTGTCCGGGT TCTGGAAGAC
60	421		GGCGCCCTC TAGGGGCGC TGCCAGGGCC CTGGCACATG GTGTCCGGGT TCTGGAAGAC
61	421		GGCGCCCTC TAGGGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
62	421		GGCGCCCTC TTAGGGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
63	421		GGCGCCCTC TAGGGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
64	421		GGCGCCCTC TAGGGGCGC TGCCAGGGCC CTGGCGCATG GCGTCCGGGT TCTGGAAGAC
65	421	GIII	GGCGCCCTC TTGGAGGCGT TGCCAGAGCT CTGCCCCACG GAGTGAGGAT TCTGGAAGAC
66	421		GGTGCCCTC TTGTGGTGT CGCCAGAGCC CTGCCCCATG GGTGAGGAT TCTGGAAGAC

Fig. 5i

CORE REGION (9/9)

21/21

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SEQUENCE
ID NUMBER GENOTYPE
=====
52 481 GI GCGGTGAAC TATGCAACAGG GAACCTTCC TGTGCTCTT TCTCTATCT CCTTCTGGCC CTGCTCTCT
53 481 GCGGTGAAC TATGCAACAGG GAACCTTCC TGTGCTCTT TCTCTATCT CCTTCTGGCC CTGCTCTCT
54 481 GCGGTGAAC TATGCAACAGG GAATCTTCC TGTGCTCTT TCTCTATCT CCTTCTGGCC CTGCTCTCT
55 481 GCGGTGAAC TATGCAACAGG GAACCTTCC TGTGCTCTT TCTCTATCT CCTTCTGGCC CTGCTCTCT
56 481 GCGGTGAAC TATGCAACAGG GAACCTTCC TGTGCTCTT TCTCTATCT CCTTCTGGCC CTGCTCTCT
57 481 GCGGTGAAC TATGCAACAGG GAACCTTCC TGTGCTCTT TTTCTATTT CCTTCTGGCC CTGCTCTCT
=====
58 481 GCGGTGAAC TATGCAACAGG GAATCTGCC GTTGTCTCT TTTCTATCT CCTCTTGGCT CTGCTGTCT
59 481 GCGGTGAAC TATGCAACAGG GAATTTGCC GTTGTCTCT TCTCTATCT CCTCTTGGCT CTGCTGTCT
60 481 GCGGTGAAC TATGCAACAGG GAATTTGCC GTTGTCTCT TCTCTATCT CCTCTTGGCT CTGCTGTCT
61 481 GCGGTGAAC TATGCAACAGG GAATCTGCC GTTGTCTCT TCTCTATCT CCTCTTGGCT TGTCTGTCT
62 481 GCGGTGAAC TATGCAACAGG GAATTTGCC GTTGTCTCT TCTCTATCT CCTCTTGGCT TGTCTGTCT
63 481 GCGGTGAAC TATGCAACAGG GAATCTGCC GTTGTCTCT TTTCTATCT CCTTCTGGCT TGTCTGTCT
64 481 GCGGTGAAC TATGCAACAGG GAATCTACC GTTGTCTCT TCTCTATCT CCTCTTGGCT TGTCTGTCT
=====
65 481 GGGTAAATT ATGCAACAGG GAATTTGCC GTTGTCTCT TCTCTATCT TCTCTTAGCC CTCTTGTCT
66 481 GGGTAAATT ATGCAACAGG GAATCTGCC
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549 Total
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C12N 15/51, 15/40, A61K 39/29 G01N 33/576, C12Q 1/68 C12Q 1/70, C07K 13/00	A3	(11) International Publication Number: WO 92/19743 (43) International Publication Date: 12 November 1992 (12.11.92)
(21) International Application Number: PCT/US92/04036 (22) International Filing Date: 8 May 1992 (08.05.92) (30) Priority data: 697,326 8 May 1991 (08.05.91) US (71) Applicant: CHIRON CORPORATION [US/US]; 4560 Horton Street, Emeryville, CA 94608 (US). (72) Inventors: CHA, Tai-An ; 964 Springview Circle, San Ramon, CA 94583 (US). BEALL, Eileen ; 1150 Lincoln Avenue, # 5, Walnut Creek, CA 94596 (US). IRVINE, Bruce ; 3401 El Monte Drive, Concord, CA 94519 (US). KOLBERG, Janice ; 131 Scots Valley, Hercules, CA 94547 (US). URDEA, Michael, S. ; 100 Bunce Meadow Road, Alamo, CA 94501 (US).		(74) Agent: JANIUK, Anthony, J.; Wolf, Greenfield & Sacks, 600 Atlantic Avenue, Boston, MA 02210 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 25 November 1993 (25.11.93)
(54) Title: HCV GENOMIC SEQUENCES FOR DIAGNOSTICS AND THERAPEUTICS (57) Abstract The present application features nucleic acid, peptide and antibody compositions relating to genotypes of hepatitis C virus and methods of using such compositions for diagnostic and therapeutic purposes.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/04036

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C12N15/51; C12Q1/68;	C12N15/40; C12Q1/70;	A61K39/29; C07K13/00
G01N33/576		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07K ; C12N ; C12Q ; A61K G01N	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	BIOCHEM. BIOPHYS. RES. COMMUN. vol. 170, no. 3, 1990, pages 1021 - 1025 N. ENOMOTO ET AL. 'There are two major types of hepatitis c in Japan' see page 1023, line 3 - page 1024, line 3; figure 1	1-4, 11-14, 17-24, 31-34, 37-44, 49 51, 52, 55-57, 59, 60, 63
X	PROC. NAT'L. ACAD. SCI. USA vol. 88, 1991, pages 3392 - 3396 N. OGATA ET AL. 'Nucleotide sequence and mutation rate of the H strain of hepatitis C virus'	1-12, 13, 17-33, 37-49, 51, 55-59, 63, 65 40-44, 49, 50, 55, 56
Y	see the whole document	

-/-		
¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 30 SEPTEMBER 1993		Date of Mailing of this International Search Report 20 OCT 1993
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer SKELLY J.M.

III. DOCUMENTS CONSIDERED TO BE RELEVANT

(CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0 388 232 (CHIRON CORPORATION) 19 September 1990 cited in the application see the whole document	40-44, 49,50, 55,56
A	JAPAN. J. EXP. MED. vol. 60, no. 3, 1990, pages 167 - 177 H. OKAMOTO ET AL. 'The 5' terminal sequence of the hepatitis C virus genome'	
A	PROC. NAT'L. ACAD. SCI. USA vol. 88, 1991, pages 2451 - 2455 Q. L. CHOO ET AL. 'Genetic organisation and diversity of the hepatitis C virus'	
X,P	WO,A,9 114 779 (MITSUI TOATSU CHEMICALS INCORPORATED) 3 October 1991 see figure 1	1-4, 11-14, 17-24, 31,33, 34, 37-44, 49,51,52 55-57, 59,60,63
X,P	WO,A,9 115 516 (GENELABS INCORPORATED) 17 October 1991 see page 93 - page 94; claim 46	1-4,11, 12,31, 32, 37-44, 49,50, 55-58,63
X	VIROLOGY vol. 180, 1991, pages 842 - 848 A.WEINER ET AL. 'Variable and hypervariable domains are found in the regions of HCV corresponding to the flavivirus envelope and NS1 proteins' see figure 1	1,2,5,6, 11,12, 17-22, 25,26, 31,32, 37-42,45 46,49, 59, 55-58, 63,64

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X,P	GB,A,2 239 245 (THE WELLCOME FOUNDATION LTD.) 26 June 1991 see the whole document	1-4, 11, 13, 17-24, 31, 33, 37-44, 49, 51, 55, 56 57, 59, 63, 65
X,P	EP,A,0 463 848 (THE RESEARCH FOUNDATION FOR MICROBIAL DISEASES OF OSAKA UNIVERSITY) 2 January 1992 see the whole document	1-4, 11, 13, 17-24, 31, 33, 37-77, 49, 51, 55, 56 57, 59, 63, 65
X,P	EP,A,0 464 287 (THE RESEARCH FOUNDATION FOR MICROBIAL DISEASES OF OSAKA UNIVERSITY) 8 January 1992 see the whole document	1-4, 11, 13, 17-24, 31, 33, 37-44, 49, 51, 55, 56 57, 59, 63, 65

INTERNATIONAL SEARCH REPORT

1. national application No.

PCT/US 92/ 04036

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See annexe 1 and annexe 2

See forms PCT/ISA/206 dated 29.10.92 and 23.04.93

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

See annexe 1
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

ANNEXE 1

1. Claims 1-4 (partially), 11 and 12, (partially), 17-24 (partially), 31 and 32 (partially), 37-44 (partially), 49 and 50 (partially), 55-58 (partially), 63 (partially): Nucleic acid having a sequence corresponding to the NS5 region of a first genotype of HCV (excluding that of the prototype HCV-1), hybridisation and detection methods using it, polypeptides encoded by it, and antibodies to the polypeptides.
2. Claims 1 and 2 (partially), 5 and 6 (partially), 11 and 12 (partially), 17-22 (partially), 25 and 26 (partially), 31 and 32 (partially), 37-42 (partially), 45 and 46 (partially), 49 and 50 (partially), 55-58 (partially), 63 (partially), 64 (partially)*:
As for subject 1, but where the nucleic acid has a sequence corresponding to the env1 region of HCV.
3. Claims 1 and 2 (partially), 7 and 8 (partially), 11 and 12 (partially), 17-22 (partially), 27 and 28 (partially), 31 and 32 (partially), 37-40 (partially), 57 and 58 (partially), 63 (partially):
As for subject 1, but where the nucleic acid has a sequence corresponding to the 5'UT region of HCV.
4. Claims 1 and 2 (partially), 9-12 (partially), 17-22 (partially), 29-32 (partially), 37-42 (partially), 47-50 (partially), 55-58 (partially), 63 and 64 (partially):
As for subject 1, but where the nucleic acid has a sequence corresponding to the core region of HCV.
5. Claims 1-12 (partially), 13, 17-32 (partially), 33, 37-50 (partially), 51, 55-58 (partially), 59, 63, 65:
Nucleic acids having a sequence corresponding to that of a second genotype of HCV, and their uses.
6. Claims 1-12 (partially), 14, 17-32 (partially), 34, 37-50 (partially), 52, 55-58 (partially), 60, 63 (partially), 66:
Nucleic acids having a sequence corresponding to that of a third genotype of HCV, and their uses.
7. Claims 1-12 (partially), 15, 17-32 (partially), 35, 37-50 (partially), 53, 55-58 (partially), 61, 63 (partially), 67:
Nucleic acids having a sequence corresponding to that of a fourth genotype of HCV and their uses.
8. Claims 1-12 (partially), 16, 17-32 (partially), 36, 37-50 (partially), 54, 55-58 (partially), 62, 63 (partially):
Nucleic acids having a sequence corresponding to that of a fifth genotype of HCV and their uses.

* Assuming that the word "envelope" has been omitted in this claim due to an error.

The applicant should note that if divisional applications directed to nucleic acids having sequences corresponding to those of the second, third, fourth and fifth genotypes are filed (subjects 5-8) they may be open to further objections of lack of unity should some of the nucleic acids already be known in the prior art.

In accordance with the warning given in the last paragraph of the original reasons for finding lack of unity, the further search of the remaining 7 subjects has in the following cases revealed prior art which leads to objections of non-unity a posteriori:

5. Nucleic acids having a sequence corresponding to that of a second genotype of HCV and their uses

A sequence 100% identical to one of the second genotype NS5 sequences (that of seq. I.D. 9) is known, see BBRC, 180, 1021, 1990, Figure 1, sequence HCV-K1-1.

Its use as a hybridisation probe is also disclosed, see Materials and Methods, last paragraph. Hence there is no longer any technical relationship between the claimed nucleic acids corresponding to the various parts of the genome of the second genotype of HCV, since they have no common technical feature which defines a contribution which each makes compared to those of the prior art.

This subject-matter can therefore be subdivided into the following separate inventions:

5a: Claims 1-4, 11, 13, 17-24, 31, 33, 37-44, 49, 51, 55-57, 59, 63 (all partially):

Nucleic acids having a sequence corresponding to the NS5 region of a second genotype of HCV, hybridisation and detection methods using it, polypeptides encoded by it and antibodies to the polypeptides.

5b: Claims 1, 2, 5, 6, 11, 13, 17-22, 25, 26, 31, 33, 37-42, 45, 46, 49, 51, 55-57, 59, 63 (all partially):

As for subject 5a, but where the nucleic acids have a sequence corresponding to the env1 sequence of a second genotype of HCV.

5c: Claims 1, 2, 7, 8, 11, 13, 17-22, 27, 28, 31, 33, 37-42, 57, 59, 63 (all partially):

As for subject 5a, but where the nucleic acids have a sequence corresponding to the 5'UT sequence of a second genotype of HCV.

5d: Claims 1, 2, 9-11, 13, 17-22, 29-31, 33, 37-42, 47, 48, 51, 55-57, 59, 63 (all partially):

As for subject 5a, but where the nucleic acids have a sequence corresponding to the core sequence of a second genotype of HCV.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

ANNEXE 2

6: Nucleic acids having a sequence corresponding to a third genotype of HCV and their uses:

A sequence 100% identical to one of the third genotype NS5 sequences (that of seq. I.D. 13) is known, see BBRC, 180, 1021, 1990, Figure 1, sequence HCV-K2a.

Its use as a hybridisation probe is also disclosed, see Materials and Methods, last paragraph.

Hence there is no longer any technical relationship between the claimed nucleic acids corresponding to the various parts of the genome of the third genotype of HCV, since they have no common technical feature which defines a contribution which each makes compared to those of the prior art.

This subject-matter can therefore also be subdivided into the following separate inventions:

6a: Claims 1-4, 11, 14, 17-24, 31, 34, 37-44, 49, 52, 55-57, 60, 63 (all partially):

Nucleic acids having a sequence corresponding to the NS5 region of a third genotype of HCV, hybridisation and detection methods using it, polypeptides encoded by it and antibodies to the polypeptides.

6b: Claims 1, 2, 5, 6, 11, 14, 17-22, 25, 26, 31, 34, 37-42, 45, 46, 49, 52, 55-57, 60, 63 (all partially):

As for subject 6a, but where the nucleic acids have a sequence corresponding to the env1 sequence of a third genotype of HCV.

6c: Claims 1, 2, 7, 8, 11, 14, 17-22, 27, 28, 31, 34, 37-42, 57, 60, 63 (all partially):

As for subject 6a, but where the nucleic acids have a sequence corresponding to the 5'UT sequence of a third genotype of HCV.

6d: Claims 1, 2, 9-11, 14, 17-22, 29-31, 34, 37-42, 47, 48, 52, 57, 60, 63 (all partially):

As for subject 6a, but where the nucleic acids have a sequence corresponding to the core sequence of a third genotype of HCV.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9204036
SA 61008

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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30/09/93

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		AU-A- 7925691	02-01-92
		CA-A- 2045323	26-12-91
		CA-A- 2045326	26-12-91
		CN-A- 1057861	15-01-92
		CN-A- 1059758	25-03-92
		EP-A- 0463848	02-01-92